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Editorial

THE ART OF CLINICAL MEDICINE : IS IT DYING?

Dr. Jayant Kumar Panda[1], Dr. Pradip Kumar Behera[2]

Medicine is learned by the bedside and not in the classroom." – Sir William Osler

As we stand at the fore-front of unprecedented technological advancements in healthcare, a fundamental question arises: is the time-honored art of clinical medicine—the direct interaction between doctor and patient, focused on physical examination and bedside care—on the verge of extinction? In an era where diagnostic technology continues to improve exponentially, are we neglecting the very skills that formed the foundation of medical practice for centuries?

For generations, clinical medicine was characterized by the physician's ability to observe, listen, and examine patients using little more than hands, eyes, and a stethoscope. However, this practice now seems endangered. Many clinicians today are caught up in a culture that prioritizes laboratory data and imaging over the direct, hands-on evaluation of the patient. While no one disputes the value of modern diagnostics, the concern remains: is the over-reliance on technology eroding the humanistic side of medical care and diminishing the role of the physician as a skilled examiner.

The Decline of Physical Examination

The practice of physical examination, once revered as the centerpiece of a physician's diagnostic abilities, has seen a steady decline in recent years. Medical students of earlier generations were meticulously trained in the art of inspection, palpation, percussion, auscultation. Detecting subtle murmurs, interpreting abnormal breath sounds, and distinguishing between upper and lower motor neuron lesions were critical skills that could make or break a diagnosis.[1] In many ways, these clinical encounters shaped the careers of physicians, not only honing their diagnostic acumen but also fostering a deep sense of connection with their patients.

However, modern-day clinical practice has taken a sharp turn away from these time-honored techniques. Studies show that the frequency and thoroughness of physical examinations are in decline, especially as imaging and laboratory testing have become more readily available. A patient may present with abdominal pain, and instead of a thorough examination, clinicians may quickly order a CT scan. While the scan may provide valuable information, it risks missing the nuances that a careful physical exam could reveal—such as tenderness, guarding, or the patient's subjective response to palpation.[2]

This decline in physical examination is not merely anecdotal. Numerous studies highlight the shift, with one study by Verghese et al. identifying that inadequate bedside examinations often lead to misdiagnoses and adverse patient outcomes.[3] Physical examination errors remain a leading contributor to diagnostic inaccuracy, particularly in emergency and critical care settings. The reality is that while technology provides incredible diagnostic detail, it cannot entirely replace the valuable information gained through touch, sight, and direct patient interaction.

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The Overuse and Misuse of Technology

Undoubtedly, technology has transformed medicine. Diagnostic tools like MRI, CT scans, and molecular tests allow us to see inside the human body in ways that were unimaginable even a few decades ago. This progress has led to early detection of diseases, more precise diagnoses, and tailored treatments, all of which contribute to improved patient outcomes.

However, this growing reliance on technology also has significant downsides. Physicians today may be overly dependent on these diagnostic tools, often ordering a battery of tests before even laying hands on the patient. Technology, while incredibly powerful, has its limitations. It cannot convey the patient's level of pain, emotional distress, or other subjective feelings that only a human interaction can reveal. More troubling is the potential for over-testing and unnecessary interventions.

As Salvatore Mangione wrote, unguided reliance on technology can lead to a vicious cycle, where one test begets another, often leading to invasive procedures, surgeries, or unnecessary treatments. He emphasizes that the overuse of technology, without the guidance of solid clinical judgment and bedside skills, can result in poor patient care outcomes. Over-reliance on testing has turned the patient encounter into a mechanical, data-driven exercise where numbers and images often replace nuanced clinical interpretation.

Another consequence of this technological shift is the alienation of the patient from the medical process. When doctors spend more time reading lab results or analyzing scans than talking to their patients, they risk losing the trust and connection that form the bedrock of the therapeutic relationship. Patients are not simply collections of organs, tissues, and symptoms—they are individuals with unique stories, experiences, and concerns that often go unnoticed when physicians are too absorbed in technology.

The Lost Art of Bedside Medicine:

One of the greatest losses in this technological era is the disappearance of the ritual of bedside medicine. Abraham Verghese and his colleagues describe this as a "transformational experience," where the simple act of physical examination fosters a bond between the doctor and patient that cannot be replicated by technology. The bedside visit, with the physician's attention fully on the patient, serves as a moment of healing in itself.

The physical examination is not only about diagnosing illness—it is a symbolic gesture that shows the patient that the doctor cares. It communicates attentiveness, empathy, and the willingness to engage in their suffering. When a doctor listens to a patient's heart or palpates their abdomen, the interaction is intimate and personal, signaling to the patient that they are being cared for and understood. This experience builds trust, and trust is a critical component of effective healthcare. The patient's willingness to follow medical advice and adhere to treatment plans depends, in large part, on their belief that their doctor has their best interests at heart.

The erosion of this bedside interaction, replaced by technological assessments, can weaken the physician-patient relationship. In today's practice, many rounds are conducted in front of computer screens, with clinicians discussing lab results and imaging while the patient sits passively on the bed. The art of clinical conversation, wherein the patient shares their story and the doctor responds with insightful questions and gentle examination, is becoming less frequent.

Physical Examination: Not Just Tradition, But Evidence-Based

One common misconception is that physical examination is an outdated or inferior form of diagnosis compared to modern technology. However, research consistently shows that the combination of a good history and physical exam remains one of the most effective tools in clinical decision-making. Studies reveal that up to 75% of diagnoses can be made based on history and examination alone. For example, the identification of jugular venous distention or the presence of crackles on lung auscultation can often provide immediate, critical information about a patient's cardiovascular or respiratory status, information that imaging or lab results may not provide in a timely fashion.

Moreover, the physical exam is often faster, more cost-effective, and can prevent unnecessary testing. When used judiciously and skillfully, it can serve as a filter, helping physicians determine which tests are truly needed and which can be avoided. This not only reduces healthcare costs but also minimizes the patient's exposure to potentially harmful procedures.

Balancing Technology with Humanism: A Path Forward

Given the undeniable importance of both technology and clinical skills, the question then becomes: how can we balance the two in modern medical practice? The answer lies in integration. Clinicians must learn to use technology as an adjunct, not a replacement, for bedside skills. Programs like those at Stanford and Johns Hopkins are already implementing this approach, emphasizing the importance of bedside medicine alongside the use of diagnostic tools.

These programs train students to master the art of physical examination while using technology to confirm, refine, or expand upon their clinical findings. By blending these two aspects of medicine, clinicians can make better decisions, improve diagnostic accuracy, and strengthen the physician-patient relationship. Ultimately, a thoughtful combination of technological expertise and hands-on examination will help preserve the humanistic side of medicine while ensuring the best possible outcomes for patients.

Conclusion

Clinical medicine, at its heart, is a human-centered practice. While the advances in technology have revolutionized healthcare and will continue to do so, they should not—and cannot—replace the essential skills of bedside medicine. Physicians must not lose sight of the fact that patients are more than just the sum of their lab results and imaging studies. They are individuals who rely on the personal touch, empathy, and attentiveness that only a skilled physician can provide.

The art of clinical medicine is not dead, but it is at risk of being overshadowed. By recognizing the value of physical examination and integrating it with modern diagnostics, we can ensure that this vital aspect of medicine not only survives but thrives in the years to come. The future of medicine depends on our ability to blend the best of technology with the timeless skills of human observation, empathy, and care.

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Original Article

CARDIOVASCULAR RISK ASSESSMENT IN WOMEN WITH SUBCLINICAL HYPOTHYROIDISM COMPARED TO EUTHYROID COHORTS : A CROSS-SECTIONAL ANALYSIS

Dr. Pooja Agarwal[1], Dr. Subhasree Mishra[2], Dr. Pradip Kumar Behera[3], Dr. K.P. Tripathy[4]

Abstract:

Background : Subclinical hypothyroidism (SH) has been implicated in increased cardiovascular risk, but its association with dyslipidemia and other markers of cardiovascular risk remains debated particularly in women.

Material and Methods : This retrospective study was carried out in the Department of Medicine, KIMS Bhubaneswar. The clinical data of female patients diagnosed with SH was retrieved from MRD along with age matched euthyroid controls. The Lipid profile and Atherogenic Index of Plasma (AIP) in both the groups were compared. The AIP was analyzed for any correlation with level of TSH.

Results : A total of 31 women diagnosed with SH were matched with 30 euthyroid controls for demographic characteristics, and their thyroid function tests, lipid profiles, and AIP levels were analyzed. Significant differences were observed in triglycerides (TG), high-density lipoprotein (HDL), and AIP levels between the two groups, with SH patients exhibiting higher TG and AIP levels, and lower HDL levels than controls. Additionally, AIP was found to correlate positively with serum-thyroid stimulating hormone (S-TSH) levels in the SH group.

Conclusion : These findings underscore the potential role of AIP as a valuable marker for assessing cardiovascular risk in women with SH, highlighting the importance of regular lipid monitoring in this population.

Key words : Dyslipidemia, Hypothyroidism, Cardiovascular risk, Atherogenic index.

Introduction :

Subclinical hypothyroidism (SH) is a condition characterized by elevated serum thyroid-stimulating hormone (S-TSH) levels, while the levels of free triiodothyronine (T3) and free thyroxine (T4) remain within normal ranges. [1]SH is more prevalent in women and is estimated to affect between 4% and 10% of the adult female population globally. While the overt form of hypothyroidism has well-documented effects on lipid metabolism and cardiovascular health, the effects of SH are less clear[.2,3]

Several studies have suggested that SH is associated with an increased risk of cardiovascular disease (CVD), potentially due to alterations in lipid metabolism, but the precise mechanisms remain under investigation. [4]Dyslipidemia, which is commonly observed in hypothyroidism, is a well-known risk factor for atherosclerosis and other cardiovascular events. However, the relationship between SH and lipid abnormalities is more ambiguous, with some studies reporting lipid changes, while others find no significant differences in lipid profiles between individuals with SH and healthy controls .[5,6]

One potential tool for assessing cardiovascular risk is the Atherogenic Index of Plasma (AIP), a logarithmic ratio of triglycerides (TG) to high-density lipoprotein cholesterol (HDL-C). This index is gaining attention due to its potential to predict cardiovascular risk more effectively than traditional lipid parameters. [4]AIP values of <0.1 indicate low risk, values between 0.1 and 0.2 suggest moderate risk, and values >0.2 indicate a high risk of cardiovascular disease .[6,7]

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In this study, we aimed to assess the lipid profiles and AIP values in women with SH, comparing them with those of euthyroid controls. Additionally, we sought to investigate the relationship between AIP and S-TSH levels in women with SH, hypothesizing that AIP could serve as a more sensitive marker of cardiovascular risk in this population.

Materials and Methods :

This prospective comparative study was conducted at the Department of General Medicine, KIMS, Bhubaneswar, from February 2022 to February 2023. The study included 31 female patients with SH and 30 euthyroid controls. Both groups were matched for age and demographic characteristics. Women aged 18–65 years diagnosed with SH, defined by elevated S-TSH levels (>4.5 mIU/L) with normal free T3 and T4 levels were included in the study. Women with overt hypothyroidism, those on lipid-lowering drugs, or with known cardiovascular disease, diabetes, or other comorbidities that could affect lipid metabolism were excluded from the study. Thirtyeuthyroid women with normal thyroid function (S-TSH between 0.4 and 4.5 mIU/L, and normal free T3 and T4 levels) were recruited from the same institution as controls and were matched for age, body mass index (BMI), and other demographic variables to minimize confounding factor. The study analyzed clinical and biochemical data, including thyroid function tests (T3, T4, and S-TSH), lipid profiles (total cholesterol, TG, HDL-C, and low-density lipoprotein cholesterol [LDL-C]), and AIP. AIP was calculated using the formula:

AIP= log(TG/HDL-C)

All participants underwent fasting blood sample collection in the morning after an overnight fast of 8-12 hours. Blood samples were processed to measure serum TG, HDL-C, total cholesterol, and LDL-C using standard enzymatic methods. Serum S-TSH, T3, and T4 levels were measured using immunoassays.

Statistical Analysis:

Data were analyzed using SPSS software (version 25.0). Continuous variables were expressed as mean ± standard deviation (SD). Differences between the SH and control groups were evaluated using t- test. Correlation analysis was performed to assess the relationship between AIP and S-TSH levels in SH patients. A p-value <0.05 was considered statistically significant.

Results:

The demographic characteristics of the study participants, including age and BMI, were similar between the SH and control groups (p > 0.05). Both groups were well-matched in terms of these variables, minimizing potential confounding effects.

Table 1: Comparison of lipid profile parameters between the study groups

Lab parameters	Participants with SCH(31)	Participants without SCH(30)	p-value
T.CHOLESTEROL	227.65	157.27	0.013
TG	248.58	137.37	0.001
HDL	34.26	36.32	0.469
LDL	103.13	99.7	0.751
VLDL	53.55	32.50	0.001
T3	2.53	2.80	0.301
T4	4.31	3.68	0.563
AIP	0.84	0.55	0.001

Women with SH had significantly higher S-TSH levels compared to euthyroid controls (6.2 ± 1.3 mIU/L vs. 2.1 ± 0.9 mIU/L, p < 0.001), as expected. However, free T3 and T4 levels were within normal ranges for both groups, confirming the diagnosis of subclinical hypothyroidism.

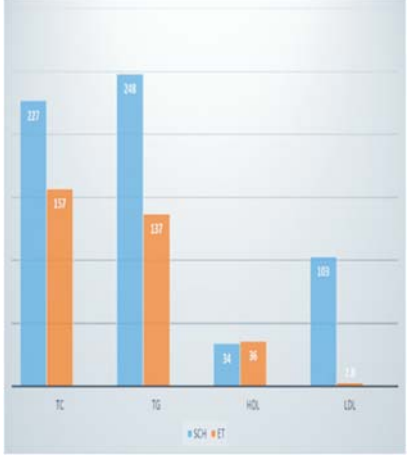

Figure 1: Comparison of lipid profile between the SCH and ET group

Women with SH had higher TG levels (248.5 ± 78.3 mg/dL) compared to the euthyroid controls (137.3 ± 48.9 mg/dL, $p < 0.001$). No significant differences were observed in HDL-C ,total cholesterol and LDL-C levels between the two groups ($p > 0.05$).

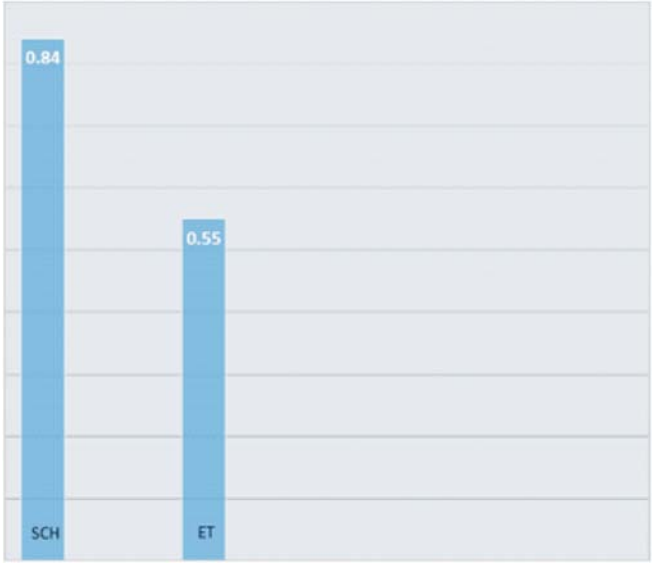

Figure 2:Comparison of AIP between the SCH group and ET group

The AIP was significantly higher in women with SH (0.56 ± 0.28) compared to euthyroid controls (0.29 ± 0.32, $p < 0.001$), indicating a higher atherogenic risk in the SH group. According to AIP categories, the majority of SH patients fell into the high-risk category for cardiovascular disease, while most euthyroid women had low or moderate AIP values

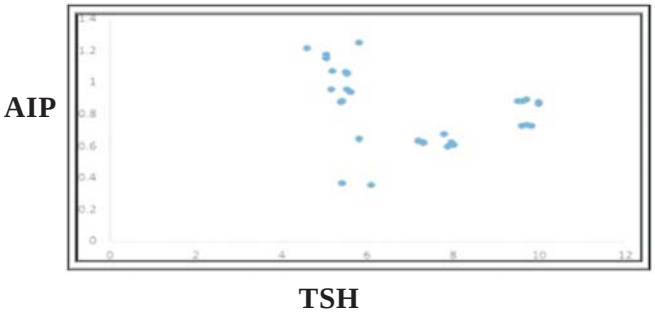

Figure 3:Correlation between AIP and TSH (r=0.43 , p value- 0.001)

A significant positive correlation was found between AIP and S-TSH levels in the SH group ($r = 0.43$, $p = 0.001$), suggesting that higher S-TSH levels may be associated with an increased atherogenic risk. This correlation underscores the potential use of AIP as a sensitive marker for cardiovascular risk in SH patients.

Discussion:

Our study supports the growing body of evidence linking SH with altered lipid metabolism and increased cardiovascular risk. We observed significantly higher TG levels and lower HDL-C levels in women with SH compared to euthyroid controls, consistent with previous studies by Satyaphalan T et al and Metalon S et al that reported similar lipid abnormalities in SH.[6,8] These changes are likely to contribute to the increased risk of atherosclerosis and other cardiovascular events in SH patients.

The AIP, a relatively new marker for assessing atherogenic risk, was significantly elevated in SH patients in our study. AIP, which reflects the balance between pro-atherogenic TGs and protective HDL-C, has been shown to predict cardiovascular risk more accurately than individual lipid parameters .[9] Our findings align with previous research by Delitala AP et al and Madhura NS et al indicating that AIP is a valuable tool for assessing cardiovascular risk, especially in populations with dyslipidemia .[10,11]

One of the key findings of our study was the positive correlation between AIP and S-TSH levels in the SH group. This suggests that as S-TSH levels rise, there is a concomitant increase in atherogenic risk, as indicated by higher AIP values. This correlation highlights the importance of monitoring both S-TSH and lipid profiles in SH patients to identify those at the highest risk of cardiovascular disease.[9,12]

While our study adds valuable insights into the relationship between SH and cardiovascular risk, it has some limitations. First, the sample size was relatively small, which may limit the generalizability of our findings. Second, the retrospective design of the study precludes the establishment of causal relationships. Future prospective studies with larger sample sizes and longer follow-up periods are needed to confirm our findings and to explore the mechanisms underlying the

relationship between SH, lipid metabolism, and cardiovascular risk.

Conclusion:

In conclusion, our study demonstrates that women with subclinical hypothyroidism exhibit significant alterations in lipid profiles, including higher triglycerides and lower HDL.Regular monitoring of lipid profiles and S-TSH levels is crucial for managing cardiovascular risk in this population, underscoring the need for further research in this area.

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Original Article

NEUTROPHIL TO LYMPHOCYTE RATIO (NLR) AS A PREDICTOR OF SEVERITY OF INFLAMMATION IN RHEUMATOID ARTHRITIS (RA)

Dr. Sasidhar Chodey[1], Dr. Debashis Pathi[2], Dr. Pradip Kumar Behera[3], Dr. K.P. Tripathy[3]

Abstract:

Background : Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease requiring accurate assessment of disease activity. This study investigates the utility of the Neutrophil-to-Lymphocyte Ratio (NLR) as a predictor of inflammation severity in RA patients.

Methods : In this prospective analytical study, 29 RA patients diagnosed according to ACR/EULAR 2010 criteria were evaluated. NLR was calculated from complete blood counts and correlated with Disease Activity Score-28 (DAS-28) using ESR.

Results : A strong positive correlation was observed between NLR and DAS-28 (ESR) (AUC 0.94, 95% CI: 0.81-1.00, p=0.008). NLR demonstrated high sensitivity (77.8%) and specificity (95.0%) in identifying high disease activity. **Conclusion:** NLR shows promise as a simple, cost-effective marker for assessing inflammation severity in RA, potentially complementing established measures like DAS-28.

Key Words : Disease Activity Score-28, Systemic Inflammation, Inflamatory Arthritis, Neutrophil to Lymphocyte Ratio.

Introduction :

Rheumatoid arthritis (RA) is a chronic, progressive autoimmune disease characterized by synovial inflammation, joint destruction, and systemic manifestations [1]. Despite extensive research, the precise aetiology of RA remains elusive, with a complex interplay of genetic, environmental, and immunological factors contributing to its pathogenesis [2]. The heterogeneous nature of RA presents challenges in diagnosis, prognosis, and management, necessitating the exploration of novel biomarkers to enhance clinical decision-making [3].

In recent years, the neutrophil-to-lymphocyte ratio (NLR) has emerged as a simple yet potentially powerful marker of systemic inflammation [4]. Derived from routine complete blood count (CBC) analyses, NLR offers a readily accessible and cost-effective means of assessing inflammatory status [5]. While traditionally associated with cardiovascular disease and malignancies, growing evidence suggests that NLR may hold significant value in autoimmune conditions, including RA [6].

The rationale for investigating NLR in RA stems from the pivotal roles of both neutrophils and lymphocytes in the disease process. Neutrophils, as key effectors of the innate immune response, contribute to synovial inflammation through the release of reactive oxygen species, proteolytic enzymes, and pro-inflammatory cytokines [7]. Conversely, lymphocytes, particularly T cells, orchestrate the adaptive immune response and are implicated in the perpetuation of synovitis and joint destruction [8]. The balance between these cell populations, as reflected by the NLR, may therefore provide insights into the overall inflammatory milieu in RA patients.

Current assessment of disease activity in RA relies heavily on composite scores such as the Disease Activity Score-28 (DAS28), which incorporates clinical, biochemical, and patient-reported measures [9]. While valuable, these scores can be time-consuming to calculate and may not always reflect the underlying inflammatory burden accurately. The potential of NLR as a complementary or alternative marker lies in its

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simplicity, objectivity, and potential to capture systemic inflammation beyond joint involvement [10].

This study aims to investigate the relationship between NLR and established measures of disease activity in RA, with a particular focus on its correlation with DAS28 scores. By exploring the utility of NLR as a predictor of inflammation severity, we seek to enhance the armamentarium of tools available for monitoring RA progression and guiding therapeutic decisions. Furthermore, understanding the association between NLR and disease activity may provide insights into the complex immunopathology of RA, potentially opening avenues for targeted interventions and personalized medicine approaches.

Materials and Methods :

Study Design and Participants

This prospective analytical study was conducted over a three-month period at the Department of Medicine and Rheumatology Clinic of KIMS. A total of 29 patients (n=29) with rheumatoid arthritis, diagnosed according to the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) 2010 criteria, were enrolled [11]. Inclusion criteria encompassed:

1. Age e" 18 years
2. Confirmed diagnosis of RA based on ACR/EULAR 2010 criteria
3. Willingness to participate and provide informed consent

Exclusion criteria were applied to minimize confounding factors and ensure the specificity of findings to RA-related inflammation. These criteria included:

1. Presence of concurrent infectious diseases
2. History of malignancy
3. Recent major surgery (within the past 3 months)
4. Use of medications known to significantly alter neutrophil or lymphocyte counts (e.g., high-dose corticosteroids)
5. Pregnancy or lactation

Data Collection:

Demographic and clinical data were collected through structured interviews and review of medical records. Information gathered included age, gender, disease duration, current medications, and comorbidities.

Laboratory Assessment :

Blood samples were obtained from all participants following a standardized protocol. Complete blood counts (CBC) were performed using an automated haematologyanalyser, providing absolute neutrophil and lymphocyte counts. NLR was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count.

Erythrocyte sedimentation rate (ESR) was measured using the Westergren method, and C-reactive protein (CRP) levels were determined by immunoturbidimetry (Beckman Coulter AU5800; Beckman Coulter Inc., Brea, CA, USA).

Disease Activity Assessment :

Disease activity was evaluated using the Disease Activity Score-28 with ESR (DAS28-ESR), a validated composite measure incorporating:

1. Number of swollen joints (out of 28)
2. Number of tender joints (out of 28)
3. ESR (mm/hour)
4. Patient's global assessment of disease activity on a visual analog scale (0-100 mm)

DAS28-ESR was calculated using the standard formula:

DAS28-ESR = 0.56 × "(TJC28) + 0.28 × "(SJC28) + 0.70 × ln(ESR) + 0.014 × GH

Where TJC28 is the 28-joint tender joint count, SJC28 is the 28-joint swollen joint count, ESR is the erythrocyte sedimentation rate, and GH is the patient's global health assessment.

Disease activity categories were defined as follows [12]:

– Remission: DAS28-ESR d" 2.6
– Low disease activity: 2.6 < DAS28-ESR d" 3.2
– Moderate disease activity: 3.2 < DAS28-ESR d" 5.1
– High disease activity: DAS28-ESR > 5.1

Statistical Analysis :

Statistical analyses were performed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation or median (interquartile range) depending on the distribution of data. Categorical

variables were presented as frequencies and percentages. The relationship between NLR and DAS28-ESR was assessed using Pearson's correlation coefficient for normally distributed data or Spearman's rank correlation coefficient for non-normally distributed data. Linear regression analysis was conducted to evaluate the predictive value of NLR for DAS28-ESR scores. Receiver operating characteristic (ROC) curve analysis was performed to determine the diagnostic accuracy of NLR in identifying patients with high disease activity (DAS28-ESR > 5.1). The area under the curve (AUC), sensitivity, specificity, and optimal cut-off values were calculated. A p-value < 0.05 was considered statistically significant for all analyses.

Results:

The study included 29 patients with rheumatoid arthritis. The mean age of the participants was 52.90 ± 11.076 years, with a median of 53.00 years (IQR: 46.00 - 61.50).

The mean DAS-28 (ESR) score was 3.93 ± 1.23, indicating moderate disease activity in the overall study population. The median DAS-28 (ESR) score was 3.600 (IQR: 2.750 - 5.200). The mean Neutrophil-to-Lymphocyte Ratio (NLR) was 5.73 ± 4.05, with a median of 4.5556 (IQR: 2.7848 - 9.1778). This wide range of NLR values suggests considerable variability in the inflammatory status among the study participants.

	NLR	DAS 28
Mean	5.74	3.93
Std. Deviation	4.05	1.24
Minimum	0.73	2.2
Maximum	15.33	5.8
95% Confidence interval of Mean	4.2 - 7.28	3.46 - 4.4

Table 1 illustrates the distribution of NLR values across different DAS-28 (ESR) categories.

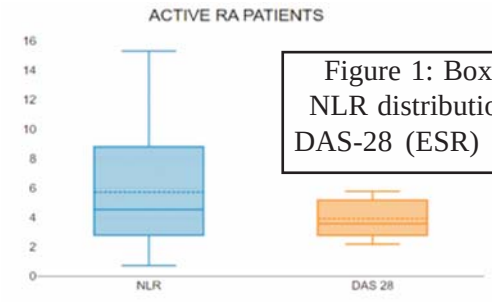
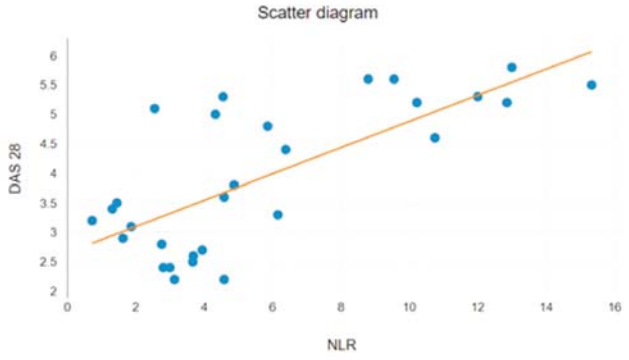


Figure 1: Box plot of NLR distribution across DAS-28 (ESR) categories

A strong positive correlation was observed between NLR and DAS-28 (ESR) scores. Figure 2 presents a scatter plot demonstrating this relationship



[Figure 2: Scatter plot of NLR vs. DAS-28 (ESR) scores]

The Receiver Operating Characteristic (ROC) curve analysis for NLR as a predictor of high disease activity yielded an Area Under the Curve (AUC) of 0.94.

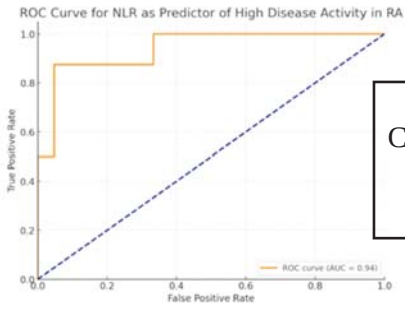
Figure 3 shows the ROC curve for NLR.

• **Pearson correlation (NLR vs. DAS 28:**Pearson correlation between NLR and DAS 28 in this study was 0.728, indicating a strong positive association between the two variables.

• This correlation was statistically significant, suggesting that higher NLR values correspond with increased DAS 28 scores, reflecting more severe disease activity in rheumatoid arthritis.

• **ROC AUC (NLR predicting high disease activity)**: 0.94, suggesting that NLR is an effective predictor of high disease activity (DAS28 > 5.1) in rheumatoid arthritis.

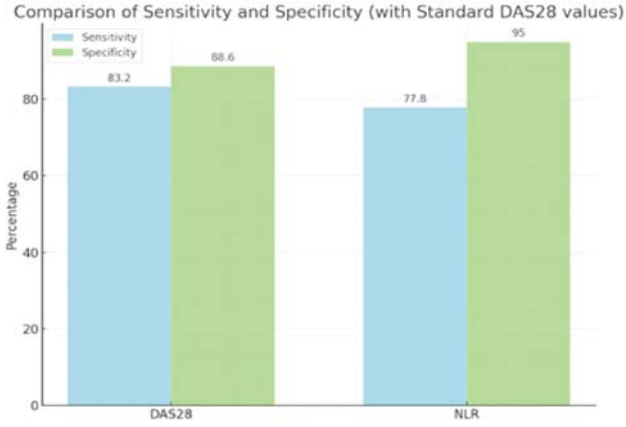
This ROC curve and AUC highlight that NLR serves as a highly accurate predictor of RA severity when compared to the DAS 28 score.



[Figure 3: ROC Curve of NLR for predicting high disease activity]

The optimal cut-off value for NLR to predict high disease activity was determined to be 7.59. At this threshold, NLR demonstrated a sensitivity of 77.8% and a specificity of 95.0%. These results suggest that NLR can effectively differentiate between patients with high disease activity and those with lower disease activity levels.

Figure 4 provides a visual comparison of the sensitivity and specificity of NLR and DAS-28 (ESR) at their respective cut-off points.



[Figure 4: Bar chart comparing sensitivity and specificity of NLR and DAS-28 (ESR)]

Discussion:

Our study demonstrates a strong positive correlation between NLR and DAS-28 (ESR) scores in patients with rheumatoid arthritis. The high AUC (0.92) obtained from the ROC analysis indicates that NLR has excellent discriminatory power in identifying patients with high disease activity. The optimal NLR cut-off value of 7.59 for predicting high disease activity showed high specificity (95.0%) and good sensitivity (77.8%). This suggests that NLR could be a valuable tool for identifying patients with severe inflammation, potentially allowing for more timely and targeted interventions. While DAS-28 (ESR) remains the gold standard for assessing disease activity in RA, our findings suggest that NLR could serve as a useful complementary measure. The simplicity and cost-effectiveness of NLR, derived from routine complete blood counts, make it an attractive option for regular monitoring of inflammatory status in RA patients.

These results align with previous studies that have explored the utility of NLR in autoimmune diseases. For instance, Mercan et al. (2016) reported a significant correlation between NLR and disease activity in both RA and ankylosing spondylitis [13]. Similarly, a meta-analysis by Erre et al. (2019) found that NLR was significantly higher in RA patients compared to healthy controls and correlated with disease activity [14]. The biological basis for the relationship between NLR and RA disease activity likely stems from the roles of neutrophils and lymphocytes in the pathogenesis of RA. Neutrophils contribute to synovial inflammation through the release of reactive oxygen species and proteolytic enzymes [15], while certain lymphocyte subsets, particularly regulatory T cells, play a crucial role in modulating the immune response [16]. The ratio between these cell populations may therefore reflect the balance between pro-inflammatory and regulatory mechanisms in RA.

Limitations and Future Directions:

Our study has several limitations. The sample size was relatively small, and the study was conducted at a single center. Future multi-center studies with larger cohorts are needed to validate these findings and establish more definitive cut-off values for NLR in different RA populations. Additionally, we did not assess the relationship between NLR and other inflammatory markers such as C-reactive protein (CRP) or pro-inflammatory cytokines. Future studies should explore these relationships to provide a more comprehensive understanding of how NLR relates to the broader inflammatory milieu in RA. Longitudinal studies are also warranted to evaluate how NLR changes over time in response to treatment and whether it can predict long-term outcomes or disease flares in RA patients.

Conclusion:

Our study provides evidence that NLR is a promising, easily obtainable marker for assessing inflammation severity in rheumatoid arthritis. Its strong correlation with DAS-28 (ESR) and high specificity in identifying high disease activity suggest that NLR could be a valuable addition to the toolkit for monitoring RA patients. While it should not replace established measures like DAS-28, NLR may offer a simple, cost-effective means of tracking inflammatory status, potentially allowing for more frequent assessments and earlier detection of disease flares.

As we continue to seek more efficient and accessible ways to monitor disease activity in RA, further research into biomarkers like NLR may pave the way for more personalized and proactive management strategies, ultimately improving outcomes for patients with this challenging chronic condition.

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Review Article

NEWER DRUGS FOR TREATMENT OF GOUT : MODERN TREATMENT FOR AN ANCIENT DISEASE

Dr. Jyoti Ranjan Parida

Abstract

Gout, characterized by the deposition of monosodium urate crystals in joints and tissues due to hyperuricemia, is a common inflammatory arthritis affecting millions worldwide. Traditional management strategies have focused on acute symptom relief and long-term urate-lowering therapy (ULT). Recent advancements in pharmacotherapy have introduced novel agents that offer alternative mechanisms of action, potentially improving outcomes for patients. This review aims to explore the latest developments in gout treatment, including emerging drugs, their mechanisms, efficacy, safety profiles, and their roles in clinical practice.

Key Words : Hyperurecimia, Urate-Lowering Therapies, Biologic Agents, Targeted Therapy

Introduction

Gout is a prevalent form of inflammatory arthritis that results from hyperuricemia, with an increasing incidence globally. The disease is characterized by sudden and severe episodes of pain, swelling, and redness in joints, often affecting the big toe (podagra). Chronic hyperuricemia can lead to the formation of tophi and may result in joint damage if left untreated. The primary goals of gout management are to relieve acute flares and to maintain serum urate levels below the solubility threshold of monosodium urate (6 mg/dL) to prevent flares and complications. Traditionally, treatments have included non-steroidal anti-inflammatory drugs (NSAIDs), colchicine, corticosteroids, and urate-lowering therapies such as allopurinol and febuxostat.

However, the limitations of these therapies, including side effects, insufficient efficacy in some patients, and adherence challenges, necessitate the exploration of new therapeutic agents. This review focuses on the latest advancements in gout management, highlighting newer drugs that have emerged as potential options for treatment.

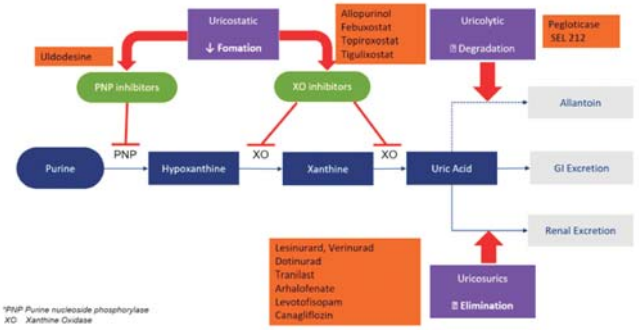

Figure 1 : Mechanism of drugs to lower serum uric acid

Newer Pharmacological Agents for Gout

In the last 2 decades, a number of new drugs have been developed for treatment of gout for both reducing acute attack and decreasing serum uric acid (Table 1). These drugs have shown clinical efficacy at least similar to or better than the existing urate lowering therapies and are expected to revolutionise the gout treatment landscape, providing effective urate-lowering capabilities with a favourable safety profile.

Table 1:Newer Pharmacological Agents for Gout

Drugs For Acute Flare	Urate lowering Therapy
IL1 Inhibitors	**Uricostatics (Decrease formation)**
Anakinra	Ulodesine
Canakinumab	Topiroxostat
Rilonacept	Tigulixostat

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Inflammasome Inhibitors	**Uricosuric agents (Increase Elimination)**
Dapansutrile	Lesinurad
	Verinurad
	Dotinurad
	Arhalofenate
	Dapaglifazone
Caspase Inhibitors	**Uricolytic Drugs (Increase degradation)**
Pralnacasan	Rasburicase
Emrlcasan	Pegloticase
	SEL 212
	Urate transporter to intestinal lumen
	ABCG2 activators

New Drugs for treatment of acute flare

1. Canakinumab :

Mechanism of Action: Canakinumab is a monoclonal antibody that targets interleukin-1â, a key mediator in the inflammatory response seen in gout.

Efficacy and Safety: Clinical trials have shown that canakinumab effectively reduces pain and inflammation during acute gout flares (Rheumatology Network, 2019). However, its use is limited by high costs and potential risks associated with immunosuppression.

2. Anakinra :

Mechanism of Action: Anakinra, an IL-1 receptor antagonist, is another biologic therapy that has been explored for acute gout flares.

Efficacy and Safety: Studies indicate that anakinra is effective in treating acute gout flares, particularly in patients with contraindications to traditional therapies (Li et al., 2015). However, its short half-life requires daily administration, which may limit patient adherence.

Urate lowering Therapy (Figure-1)

1.Topiroxostat :

Mechanism of Action :

Topiroxostat is a novel xanthine oxidase inhibitor developed as an alternative urate-lowering therapy (ULT) for patients with gout. It is designed to reduce serum uric acid levels by inhibiting the enzyme xanthine oxidase, similar to allopurinol and febuxostat, but with some unique pharmacological properties. It effectively decreases uric acid production, leading to lower serum urate levels and reduced risk of gout flares and complications.

Clinical Efficacy :

In several randomized controlled trials, topiroxostat has been shown to achieve target uric acid levels (<6 mg/dL) in a significant proportion of patients, comparable to existing therapies like allopurinol and febuxostat.One pivotal trial indicated that topiroxostat was effective in reducing uric acid levels in patients with primary gout, showing a dose-dependent response (Tanaka et al., 2015). The trial reported that a majority of patients achieved target levels within 12 weeks of treatment.This drug is approved in Japan for treatment of Gout since 2013.

Comparison with Other ULTs :

When compared to allopurinol and febuxostat, topiroxostat has shown similar efficacy in achieving uric acid target levels. However, its unique pharmacokinetic properties—such as a longer half-life and a more favorable dosing schedule (once daily) may improve patient adherence. Unlike allopurinol, which requires dose adjustments in renal impairment, topiroxostat may be better tolerated in patients with varying degrees of renal function.

Safety Profile :

The safety profile of topiroxostat appears favorable compared to traditional ULTs. Common adverse effects reported include nausea, diarrhoea, allergic skin reactions, eczema and liver enzyme elevation

2. Tigulixostat :

Mechanism of Action :

Tigulixostat is a novel, selective xanthine oxidase inhibitor developed for the management of hyperuricemia in patients with gout. It represents a new class of urate-lowering therapy (ULT), aiming to provide effective control of uric acid levels while minimizing side effects associated with traditional treatments. By selectively blocking this enzyme, tigulixostat effectively decreases uric acid production, leading to lower serum

urate levels, which can prevent gout flares and complications associated with chronic hyperuricemia.

Clinical Efficacy :

Clinical trials have shown that tigulixostat significantly lowers serum uric acid levels, with a substantial proportion of patients achieving the target level of <6 mg/dL. In one study, over 70% of patients reached this target after 12 weeks of treatment (Li et al., 2021).

Comparison with Traditional ULTs :

When compared to allopurinol and febuxostat, tigulixostat has demonstrated comparable or superior efficacy, particularly in patients who may not tolerate or adequately respond to standard therapies.

Safety Profile :

The safety profile of tigulixostat has been favorable in clinical trials:The most frequently reported side effects include gastrointestinal symptoms (nausea, diarrhea) and mild elevation in liver enzymes. These effects are generally transient and manageable. It has been associated with fewer renal-related adverse events compared to some traditional ULTs, making it a potentially safer option for patients with renal impairment.

Tigulixostat is a promising addition to the treatment landscape for gout, offering effective urate-lowering capabilities with a favorable safety profile. Its selective action and potential benefits for patients with renal impairment make it an attractive alternative for managing hyperuricemia in gout.

3. Uldedosine :

Mechanism of Action: Uldedosine inhibits PNP enzyme which convert purine to hypoxanthine and critical in the production of uric acid from purines. By blocking this enzyme, uldedosine decreases uric acid production, thereby lowering serum urate levels and reducing the risk of gout attacks.

Clinical Efficacy: Studies indicate that uldedosine is effective in significantly lowering serum uric acid levels, with many patients achieving target levels of <6 mg/dL.In a phase 2 study, 3 doses (40 mg/80mg /120 mg) reduce SUA by 2.7/ 3.3/ 4.4 mg/dl respectively and 33%, 36%, and 31% of patients achieved an SU level <6.0 mg/dL. Another advantage is it can be combined with allopurinol in patients who failed on monotherapy.Combination therapy result in a greater proportion of subjects achieving SUA < 6 mg/dL (40%, 50%, 46%, and 55%) Vs 25% in allopurinol-placebo group. Despite the potential, no ongoing trial are currently registered for this trial.

Safety Profile: The most frequently reported side effects include mild gastrointestinal disturbances, such as nausea and diarrhea. These side effects are generally well-tolerated and self-limiting.Uldedosine is considered safe for patients with mild to moderate renal impairment, a significant advantage over some traditional therapies that require careful dose adjustments.

4. Lesinurad :

Mechanism of Action: Lesinurad is a selective uric acid reabsorption inhibitor that increases uric acid excretion by inhibiting the URAT1 transporter in the kidneys.

Efficacy and Safety: In combination with allopurinol, lesinurad has been shown to significantly reduce serum uric acid levels and decrease gout flare frequency (Kivitz et al., 2016). The combination group able to maintain sUA lowering for up to 2 yrs. It also continued to enhance tophi resolution, reduce tophus size, and decrease gout flares.

Safety Profile: The most common adverse effects include renal-related events, particularly in patients with existing renal impairment and it is contraindicated in serum creatinine clearance <30 ml/ min.

5. Dapagliflozin :

Mechanism of Action: Dapagliflozin works by inhibiting the SGLT2 transporter in the proximal renal tubules, leading to increased urinary glucose excretion and reduced blood glucose levels. Additionally, it may have several indirect effects relevant to gout **management:**

Uric Acid Excretion: SGLT2 inhibitors, including dapagliflozin, can promote renal uric acid excretion, thereby lowering serum uric acid levels. This mechanism may help prevent gout flares.

Weight Loss and Improved Metabolic Profile: The drug may aid in weight loss and improve overall metabolic health, which can indirectly benefit gout management.

Clinical Efficacy: Recent studies have begun to assess the effectiveness of dapagliflozin in patients with gout.Dapagliflozin can significantly reduce serum uric acid levels in patients, with some studies showing a reduction sufficient to lower the risk of gout attacks (Sonnenschein et al., 2021). The QUARTZ study has clearly demonstrated the efficacy of dafaglifazone in addition to verinurad and febuxostat in decreasing serum uric acid. Some observational studies suggest that dapagliflozin may reduce the frequency of gout flares in patients with diabetes or CKD, although more robust clinical trial data are needed to confirm these findings.

Safety Profile: Dapagliflozin is generally well-tolerated, with a safety profile consistent with other SGLT2 inhibitors. The most frequently reported side effects include urinary tract infections, genital mycotic infections, and mild dehydration. It is considered safe for patients with mild to moderate renal impairment, although caution is warranted in those with severe renal dysfunction.

6. Rasburicase :

Mechanism of Action: Rasburicase is the prototypical recombinant Fungal uricase. It is approved for the treatment of hyperuricemia in malignancy and tumor lysis syndrome. The typical dose is 2.0 mg/kg IV daily for 1-5 days based on clinical symptoms

Clinical Efficacy: It has potent and rapid urate-lowering effect superior to allopurinol (start within 4hours of administration).

Safety Profile: Usually well- tolerated (black-box warning for anaphylaxis, hemolysis, and methemoglobinemia). Anti-rasburicase antibodies in seen 11–64% of patients. Repeat courses of rasburicase are not recommended (increased rate of anaphylaxis).Rasburicase is not a preferred agent for long-term management of gout due to limited therapeutic indication, cost, and route of administration.

7. Pegloticase :

Mechanism of Action: Pegloticase is a recombinant uricase enzyme that catalyzes the conversion of uric acid to allantoin, a more soluble compound that is easily excreted by the kidneys.

Efficacy and Safety: Clinical trials have demonstrated that pegloticase effectively lowers uric acid levels in patients with treatment-resistant gout. In a pivotal study, 42% of patients achieved and maintained target uric acid levels for at least six months (Sivera et al., 2014).

Safety Profile: Pegloticase is associated with infusion reactions and the development of anti-drug antibodies, which can limit its long-term use.There are many strategies developed to decrease the immunogenicity like coadministration with other immunomodulatory drugs like methotrexate, azathioprine and mycophenolate or alternate dosing regimen

Conclusion:

The landscape of gout management is evolving with the introduction of newer pharmacological agents that offer alternative therapeutic options for patients. While traditional therapies remain essential, newer agents such as pegloticase, lesinurad, and biologics provide opportunities for improved outcomes, particularly in patients with treatment-resistant gout or those who experience side effects from conventional treatments. Ongoing research is critical to further elucidate the long-term efficacy and safety profiles of these agents and to refine treatment strategies for optimal patient care.

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Review Article

RECENT ADVANCES IN THE DIAGNOSIS AND TREATMENT OF MULTIPLE MYELOMA : A BRIEF REVIEW

Dr. K.P. Tripathy[1], Dr. Santosh Kumar Swain[2], Dr. Pradip Kumar Behera[3], Dr. Mahesh STV[4]

Abstract :

Multiple myeloma (MM), a hematologic malignancy characterized by clonal proliferation of plasma cells in the bone marrow, represents a complex disease with significant morbidity and mortality. Despite advancements in its diagnosis and management, it remains incurable in most cases. Recent developments, however, have considerably improved the outlook for patients. This review provides an updated summary of the pathophysiology, diagnostic tools, and emerging therapies for MM, with a focus on new molecular markers, advanced imaging techniques, and novel therapeutic agents, including immunotherapies and personalized treatments. The evolving landscape of MM management suggests that the integration of these novel approaches will continue to improve patient outcomes.

Key Words : Multiple Myeloma, Novel Therapies, Biomarkers, Immunotherapy, Targeted Treatment

Introduction :

Multiple myeloma (MM) is the second most common hematologic malignancy in adults, characterized by the abnormal proliferation of clonal plasma cells in the bone marrow. Multiple myeloma accounts for approximately 10% of hematologic malignancies and primarily affects older adults. The disease arises from malignant plasma cells that accumulate in the bone marrow, leading to bone destruction, renal impairment, anemia, and immune suppression. While high-dose chemotherapy and Autologous stem cell transplantation (ASCT) have been the cornerstone of treatment, recent innovations, particularly in targeted therapies and immunotherapy, have revolutionized the field. This review discusses key updates in the diagnosis and treatment of MM, focusing on the most recent research findings and clinical applications.

1. Pathophysiology of Multiple Myeloma:

Multiple myeloma is characterized by the uncontrolled proliferation of clonal plasma cells in the bone marrow. These malignant cells secrete monoclonal immunoglobulins (M-protein), which can be detected in the blood and urine, contributing to organ dysfunction and clinical manifestations such as hypercalcemia, renal failure, anemia, and bone lesions (CRAB criteria) . Several factors contribute to the development and progression of MM, including genetic abnormalities, epigenetic alterations, and interactions within the bone marrow microenvironment.(Fig. 1)

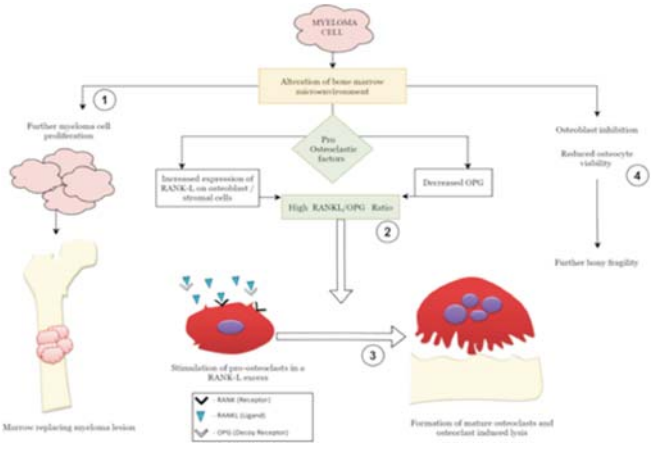

Fig. 1 Mechanism underlying development of Multiple Myeloma.

Key molecular alterations frequently observed in MM include :

– **Chromosomal abnormalities**: Translocations involving the immunoglobulin heavy chain locus

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(e.g., t(4;14), t(11;14)), deletion 17p, and hyperdiploidy.

– **Oncogene mutations**: Mutations in NRAS, KRAS, and BRAF play a role in the clonal evolution of MM .
– **Epigenetic changes**: Modifications of DNA methylation and histone acetylation are increasingly recognized as contributors to myelomagenesis .
– **Bone marrow microenvironment**: Interactions between myeloma cells and the bone marrow niche, including stromal cells, osteoclasts, and the extracellular matrix, facilitate tumor growth, survival, and resistance to therapy .

Recent studies have identified several potential therapeutic targets in MM, including signaling pathways (e.g., PI3K-Akt, NF-êB, JAK-STAT) and cell surface receptors (e.g., SLAMF7, BCMA) .

2. Advances in Diagnosis of Multiple Myeloma :

Timely and accurate diagnosis of MM is crucial for optimizing patient outcomes. Recent advances in diagnostic techniques have improved the ability to detect MM at earlier stages and to stratify patients based on risk.

2.1. Biomarkers:

– **Next-generation sequencing (NGS):** NGS has provided a more detailed understanding of the genomic landscape of MM. It is used to identify high-risk mutations and track clonal evolution during treatment.
– **Minimal residual disease (MRD) detection**: MRD, assessed using either flow cytometry or NGS, has emerged as a critical tool for monitoring treatment response and guiding therapy. MRD negativity has been associated with prolonged progression-free and overall survival.
– **Circulating tumor cells and cell-free DNA**: Emerging technologies that detect circulating myeloma cells or tumor DNA in peripheral blood offer a non-invasive method to monitor disease progression and treatment response.

2.2. Imaging Techniques:

– Magnetic resonance imaging (MRI) and positron emission tomography-computed tomography (PET-CT) have become integral to MM diagnosis and staging. PET-CT, in particular, can detect active myeloma lesions and assess response to therapy .
– Whole-body low-dose CT is increasingly used to evaluate bone disease, offering higher sensitivity than conventional skeletal surveys .

3. Risk Stratification :

Risk stratification plays a key role in tailoring treatment strategies for MM. Patients are categorized into risk groups based on clinical features, cytogenetics, and molecular markers.(Table 1)

STANDARD RISK	INTERMEDIATE RISK	HIGH RISK
1. Trisomies (hyperdiploidy) - Presence of 48–74 chromosomes harboring numerous chromosomal trisomies - Associated with advanced age, bone involvement at presentation, and favorable outcome -Excellent response to lenalidomide-based therapy	**1. t (4;14)** -Associated with IgA heavy chain disease and λ light chain disease - High prevalence of coexistent chromosome 13 abnormalities - Increased expression of FGFR3 and MMSET (multiple myeloma SET domain) gene - Needs bortezomib-based initial therapy and early ASCT	**1. 17p deletion** -Associated with extramedullary disease and plasma cell leukemia
2. t (11;14) -Associated with lymphoplasmacytic morphology,CD20 expression, oligosecretory and light chain disease, upregulation of cyclin D1	**2. Gain(1q21)** -Associated with aggressive features like extensive bony, extramedullary, and CNS, involvement - Worse prognosis despite novel agents based therapies	**2. t (14;16)** -Acute renal failure as initial event - Associated with higher frequency of ch 13 deletion, IgA isotype and aggressive clinical course
3. t (6;14) - IgH gene traslocation occurs with the cyclin D3 gene (6p21) Most have myeloma bone disease at diagnosis		**3. t (14;20)** -The least common primary genetic abnormalities in MM with prevalence of <1%
4 . Normal -Reflect low tumor burden; thus considered as standard/low risk		**4. High risk gene expression profiling signature** -Bi-allelic TP53 inactivation Amplification (≥ 4 copies) of CKS1B (1q21) Taken together, recently categorized as "Double Hit Myeloma"

3.1. Revised International Staging System (R-ISS):

The R-ISS incorporates serum â2-microglobulin, albumin, lactate dehydrogenase (LDH), and chromosomal abnormalities (e.g., del(17p), t(4;14), t(14;16)) to stratify patients into three risk categories (I, II, and III) .

Revised International Staging System (R-ISS)

Stage	Criteria
I	Sâ2M < 3.5 mg/lSerum albumin e" 3.5 g/dlStandard-risk chromosomal abnormalities (CA) by iFISHNormal LDH
II	Not R-ISS stage I or III
III	Sâ2M e" 5.5 mg/L and eitherHigh-risk CA by FISHORHigh LDH

3.2. Genetic and Molecular Markers :

Cytogenetic abnormalities detected by fluorescence in situ hybridization (FISH) are routinely used to guide treatment decisions. High-risk genetic features such as del(17p), t(4;14), and gain(1q21) are associated with poor outcomes .

4. Emerging Therapeutic Approaches :

The treatment landscape for MM has evolved significantly with the introduction of novel agents. Standard therapeutic options include proteasome inhibitors, immunomodulatory drugs, and monoclonal antibodies. However, new therapies are rapidly gaining attention, offering promising results.

4.1. Immunotherapy :

Immunotherapy for multiple myeloma is a promising new treatment option, with the potential to result in long-term cancer remission similar to the results of allogeneic bone marrow transplantation with less risk for complications.

4.1.1. Monoclonal Antibodies :

The recent development of monoclonal antibodies (mAbs) has revolutionized the treatment armamentarium for multiple myeloma. The success of daratumumab and elotuzumab in relapsed/refractory patients, has generated tremendous enthusiasm for mAbs in this disease.

– **Daratumumab**: A monoclonal antibody targeting CD38, daratumumab has shown efficacy both as a monotherapy and in combination with standard regimens .

– **Elotuzumab**: Targeting SLAMF7, elotuzumab is used in combination with lenalidomide and dexamethasone for relapsed MM .

– **Isatuximab**: Another anti-CD38 antibody, isatuximab has demonstrated significant activity in patients with relapsed or refractory MM .

4.1.2. Bispecific T-cell engagers (BiTEs):

Bispecific T cell engagers (TCE) derive from monoclonal antibodies and concomitantly engage a target on the surface of cancer cell and CD3 on the surface of T-cells. TCEs promote T cell activation and lysis of tumor cells. Most TCEs in development for multiple myeloma (MM) target the B cell maturation antigen (BCMA) .Teclistamab, a BCMA-targeting BiTE, has shown promising efficacy in clinical trials for relapsed/refractory MM .

4.1.3. Chimeric Antigen Receptor (CAR) T-cell Therapy :

CAR T-cell therapy has emerged as a game-changer in treating multiple myeloma (MM). This novel treatment method complements options like autologous stem cell transplants and immunomodulatory medications, such as proteasome inhibitors, by utilizing protein complexes or anti-CD38 antibodies with potent complement-dependent cytotoxic effects. CAR T-cell therapy, particularly against B-cell maturation antigen (BCMA), has shown remarkable efficacy in heavily pretreated MM patients. Idecabtagene vicleucel (ide-cel) and Ciltacabtagene autoleucel (cilta-cel) are BCMA-directed CAR T-cell therapies that have demonstrated durable responses in clinical trials .

4.2. Proteasome Inhibitors :

Proteasome inhibitors, such as bortezomib and carfilzomib, remain essential components of MM therapy. The second-generation inhibitor ixazomib offers the advantage of oral administration, improving patient convenience and compliance .

4.3. Immunomodulatory Drugs (IMiDs) :

IMiDs such as lenalidomide and pomalidomide have become the backbone of MM treatment. These agents modulate the immune system, enhance anti-tumor activity, and inhibit angiogenesis.

4.4. Targeted Therapies :

– **Selinexor**: A selective inhibitor of nuclear export, selinexor has shown efficacy in patients with refractory MM, particularly when combined with other agents.

– **Venetoclax:** A BCL-2 inhibitor, venetoclax has shown promising activity in patients with t(11;14)-positive MM.

4.5. Novel Small Molecules :

Several novel small molecules targeting critical signaling pathways in MM are under investigation. For instance, inhibitors of the PI3K/Akt/mTOR pathway, BTK inhibitors, and epigenetic modulators such as BET inhibitors are in various stages of clinical trials .

5. Transplantation and Maintenance Therapy :

5.1. Autologous Stem Cell Transplantation (ASCT) :

High-dose chemotherapy followed by ASCT remains the standard of care for eligible MM patients. ASCT offers prolonged progression-free survival but is not curative. Recent studies suggest that tandem ASCT may benefit high-risk patients .

5.2. Maintenance Therapy :

Maintenance therapy with lenalidomide or bortezomib after ASCT has been shown to prolong progression-free survival . Ongoing studies are exploring the role of newer agents, including monoclonal antibodies, in maintenance therapy .

6. Management of Relapsed and Refractory Multiple Myeloma (RRMM) :

Despite initial responses to treatment, most MM patients eventually experience relapse. The management of relapsed/refractory MM (RRMM) requires a tailored approach based on prior treatments, patient comorbidities, and the availability of new agents.

6.1. Treatment Options for RRMM :

– Rechallenge with previously effective regimens (e.g., bortezomib or lenalidomide) in combination with new agents.

– Use of novel therapies such as CAR T-cell therapy, BiTEs, and selinexor in heavily pretreated patients .

6.2. Emerging Combination Therapies :

The use of triple or quadruple combination regimens, incorporating novel agents (e.g., proteasome inhibitors, IMiDs, and monoclonal antibodies), is increasingly common in the treatment of RRMM .

7. Future Directions and Ongoing Challenges :

While significant progress has been made in the management of MM, challenges remain. The disease is still incurable for most patients, and long-term survival is often limited by relapse and the development of drug resistance. Ongoing research efforts aim to improve outcomes by further understanding the molecular mechanisms of MM and developing therapies that can overcome resistance.

One key area of future research is the continued exploration of MRD as a marker for treatment success. The use of MRD negativity as a treatment goal may enable more personalized approaches, allowing for treatment intensification in high-risk patients and de-escalation in those with low-risk disease.

Additionally, novel therapies such as CAR T-cell therapies and bispecific antibodies are showing promise in clinical trials, but there remain logistical and financial challenges to widespread implementation. The development of “off-the-shelf” CAR T-cell products and improved manufacturing processes may help address these issues.

Conclusion:

Multiple myeloma has experienced remarkable advances in diagnosis and treatment over the past decade. New diagnostic tools, such as MRD detection and advanced imaging techniques, have improved risk stratification and monitoring. Therapeutic advances, including novel immunotherapies and small molecules, have expanded treatment options and improved outcomes for many patients. However, MM remains a largely incurable disease, and ongoing research into its pathophysiology, resistance mechanisms, and novel therapies is critical to further improving survival and quality of life for affected individuals.

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Case Report

FEVER AND RASH AS CLUES : UNCOVERING BAZIN'S DISEASE : A RARE FORM OF CUTANEOUS TUBERCULOSIS

Dr. Biswajit Mohanty[1], Dr. Niranjan Mohapatra[2], Dr. Jayant Kumar Panda[3]

Introduction :

Bazin's disease, also known as erythema induratum, is a rare form of cutaneous tuberculosis primarily affecting the lower extremities. First described by Ernest Bazin in the 19th century, it presents as tender, erythematous nodules, which may ulcerate over time. Though Mycobacterium tuberculosis is the underlying pathogen, the disease's cutaneous manifestations are uncommon. Diagnosing Bazin's disease poses a challenge due to its nonspecific symptoms, such as fever and rash, which mimic various other dermatological and systemic conditions.

The pathogenesis of Bazin's disease is thought to involve a hypersensitivity reaction to tubercular antigens, rather than direct bacterial invasion of the skin. Consequently, diagnosis requires a combination of clinical suspicion, histopathology, and microbiological evidence, including PCR and tuberculin skin testing. Early recognition is crucial, as delayed diagnosis can lead to complications, including chronic ulceration and scarring.

This case report highlights a rare presentation of Bazin's disease in a patient with prolonged fever and rash. It underscores the importance of considering cutaneous tuberculosis in the differential diagnosis of persistent dermatological lesions, particularly in endemic areas or individuals with risk factors for tuberculosis.

Case Presentation:

A 40-year-old female from rural Odisha presented to the medicine OPD with chief complaints of low-grade fever for the past 4 months. She also reported a typical evening rise in temperature for the last month. Additionally, she noticed nodular rashes with erythematous bases on both her legs (anterior and posterior compartments) for the past 3 months, some of which were painful at onset. In the last month, similar rashes developed on the ventral aspects of both forearms. She also complained of significant weight loss. She denied symptoms of alopecia, joint pain, oral ulcers, cough, or diarrhea. She was not on any oral contraceptives or other medications. There was no history of comorbidities, tuberculosis exposure, or family history of malignancy.

Upon admission for further evaluation, a head-to-toe examination revealed multiple nodular erythematous rashes of varying sizes on both legs and two on her forearms. Some of these lesions were tender, and others were indurated. Systemic examinations were otherwise unremarkable.

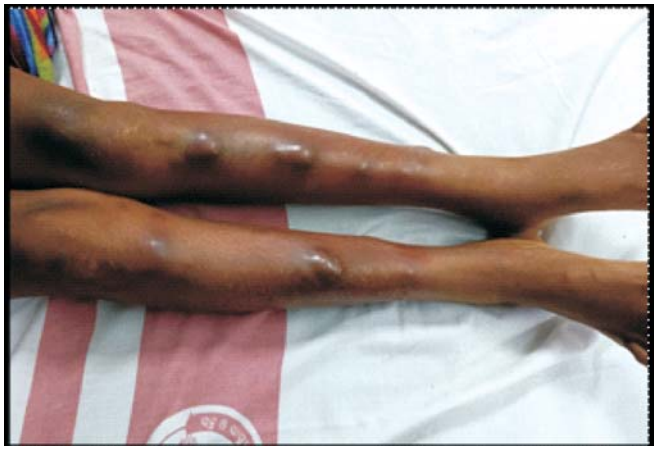

Figure: Erythematous nodular lesions over front of both legs

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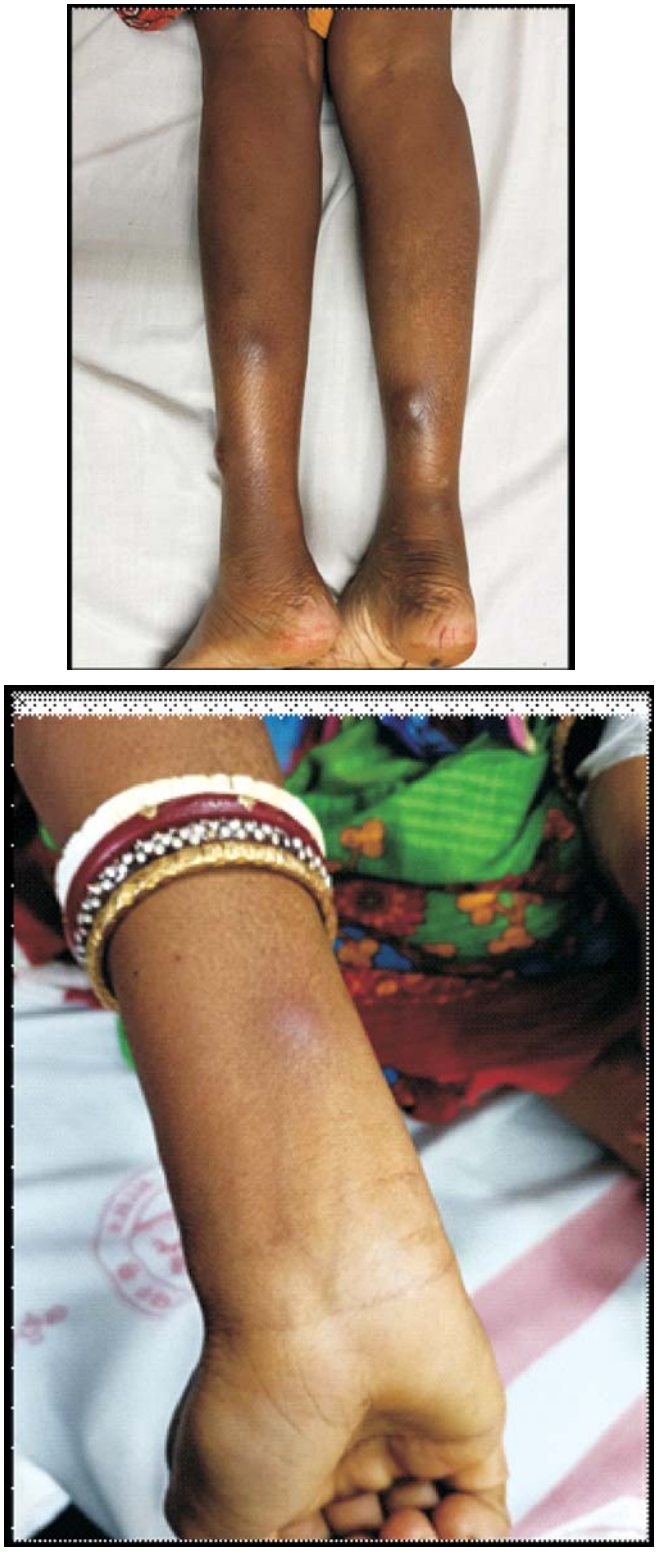

Figure: Erythematous nodular lesions over the legs and forearm

A routine hemogram revealed moderate anemia (peripheral smear showed a microcytic, hypochromic pattern) along with a persistently elevated ESR. Liver and renal function tests were within normal limits. A routine chest X-ray revealed no abnormalities. The Coomb's test was negative, and the serum iron profile indicated anemia of chronic disease. Serum angiotensin-converting enzyme levels were normal, and ANA was negative. While the fever subsided with antipyretics, the ESR remained persistently high, and the rashes continued.

In suspicion of erythema nodosum, a skin biopsy was performed on a rash over the shin. The skin biopsy revealed mild perivascular chronic inflammation characterized by lymphocytes and plasma cells in the superficial dermis. The deep dermis exhibited collagen bundles with foci of interstitial mucin deposition. The subcutaneous fat showed features of lobular panniculitis with dense lymphohistiocytic infiltrates along the lobules and septa. Vague granulomas were observed in certain areas. All these findings were consistent with erythema induratum of Bazin, or Bazin's disease.

Treatment and Follow up :

The patient was started on anti-tubercular therapy (ATT). One month after the initiation of ATT, her fever had subsided, and the rashes began to diminish. By her third follow-up, all her rashes had resolved. She completed ATT according to the National Tuberculosis Elimination Program (NTEP) guidelines.

Discussion :

Bazin's disease, or erythema induratum, is a rare type of tuberculid primarily affecting middle-aged women. It is considered a hypersensitivity reaction to Mycobacterium tuberculosis, rather than a direct bacterial infection of the skin. Typically presenting as painful nodules on the lower extremities, it may mimic other conditions such as erythema nodosum, vasculitis, or sarcoidosis. The lack of specificity in clinical presentation often leads to diagnostic delays, as was observed in this case.

The diagnosis of Bazin's disease requires a high degree of clinical suspicion, supported by histopathological findings. Histology typically reveals lobular panniculitis with caseation necrosis, a hallmark feature of this condition. Although direct detection of

M. tuberculosis in skin lesions is rare, PCR and tuberculin skin testing often aid in diagnosis.Treatment primarily involves antitubercular therapy (ATT), which leads to resolution of lesions. In our patient, ATT was initiated following confirmation of tuberculosis through histopathology, leading to significant clinical improvement. Early diagnosis is essential to prevent chronic ulceration and scarring. This case highlights the need to consider cutaneous tuberculosis in patients presenting with persistent dermatological symptoms, especially in those with risk factors or in endemic regions.

Conclusion:

Bazin's disease, though rare, should be considered in patients with unexplained cutaneous nodules, particularly in those with a history or risk of tuberculosis. This case highlights the complexity of diagnosing atypical forms of tuberculosis and the need for vigilance in recognizing its varied presentations. Early diagnosis, supported by histopathology and microbiological tests, allows for effective treatment with antitubercular therapy, leading to favorable outcomes. This report emphasizes the significance of a broad differential diagnosis when evaluating persistent skin lesions, ensuring timely and appropriate management of rare diseases like Bazin's.

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Case Report

PRIMARY ADRENAL INSUFFIENCY IN A 32 YEAR MALE : A RARE CASE REPORT

Dr. Debasish Dhal[1], Dr. Sanjay Kumar Jangid[2]

Abstract :

Adrenal insufficiency (AI) is a medical condition characterized by adrenal cortex hypofunction, specifically inadequate cortisol production to meet the demands of significant physiological stress. We report a case of 32 year male who presented with the complaints of loss of weight and gradual darkening of skin colour since 7 months and on evaluation was found to have low serum cortisol . After ruling out other causes of adrenal insufficiency, he was diagnosed as Primary adrenal insufficiency. He improved dramatically with hormone replacement therapy. Early recognition and prompt therapy is essential for improved outcomes in this not so common ailment.

Keywords : Hyperpigmentatation, Corticosteroids, Primary Adrenal Insufficiency, Hormone Replacement Therapy

Introduction : The adrenal cortex produces three classes of corticosteroid hormones: glucocorticoids (e.g., cortisol), mineralocorticoids (e.g., aldosterone), and adrenal androgen precursors (e.g., dehydroepiandrosterone [DHEA]) . Primary AI results from intrinsic pathology of both adrenal glands with a prevalence of 2 in 10,000. Here mineralocorticoid, Adrenal androgen secretion are also disrupted .

Case Description :

We report a case of 32 year Muslim male who presented to our hospital with the chief complaints of loss of weight (72 kg to 48 kg) and gradual darkening of skin colour since 7 months, generalised body ache, severe weakness, giddiness on standing, lower back and leg pain since 5 months, constipation since 1 month. On examination he was conscious, oriented, Blood pressure – 86/ 54 mm Hg in right arm sitting position, pulse rate – 120 per minute regular. He was admitted to general ward and was started with intravenous fluids and supportive measures. All routine investigations were sent. His serum sodium was 124.9mmol/L, potassium 6.47mmol/L, urea 46 mg/dl and creatinine 1.30 mg/dl , Usg abdomen showed prominent peripancreatic lymphnodes, serum cortisol 0.413 ug/dl, on ABG analysis pH – 7.26 , bicarbonate-17.1 mmol/L . CT SCAN ABDOMEN showed atrophied bilateral adrenal glands, quantiferon TB gold test was negative. He was then treated with hormone replacement therapy with tab Hydrocortisone 10mg immediately on getting up , 5 mg at 12 pm, 5 mg at 6 pm, tab fludrocortisone 100 mcg od and was discharged . Then his treatment is being currently monitored with assessment of body weight and blood pressure.

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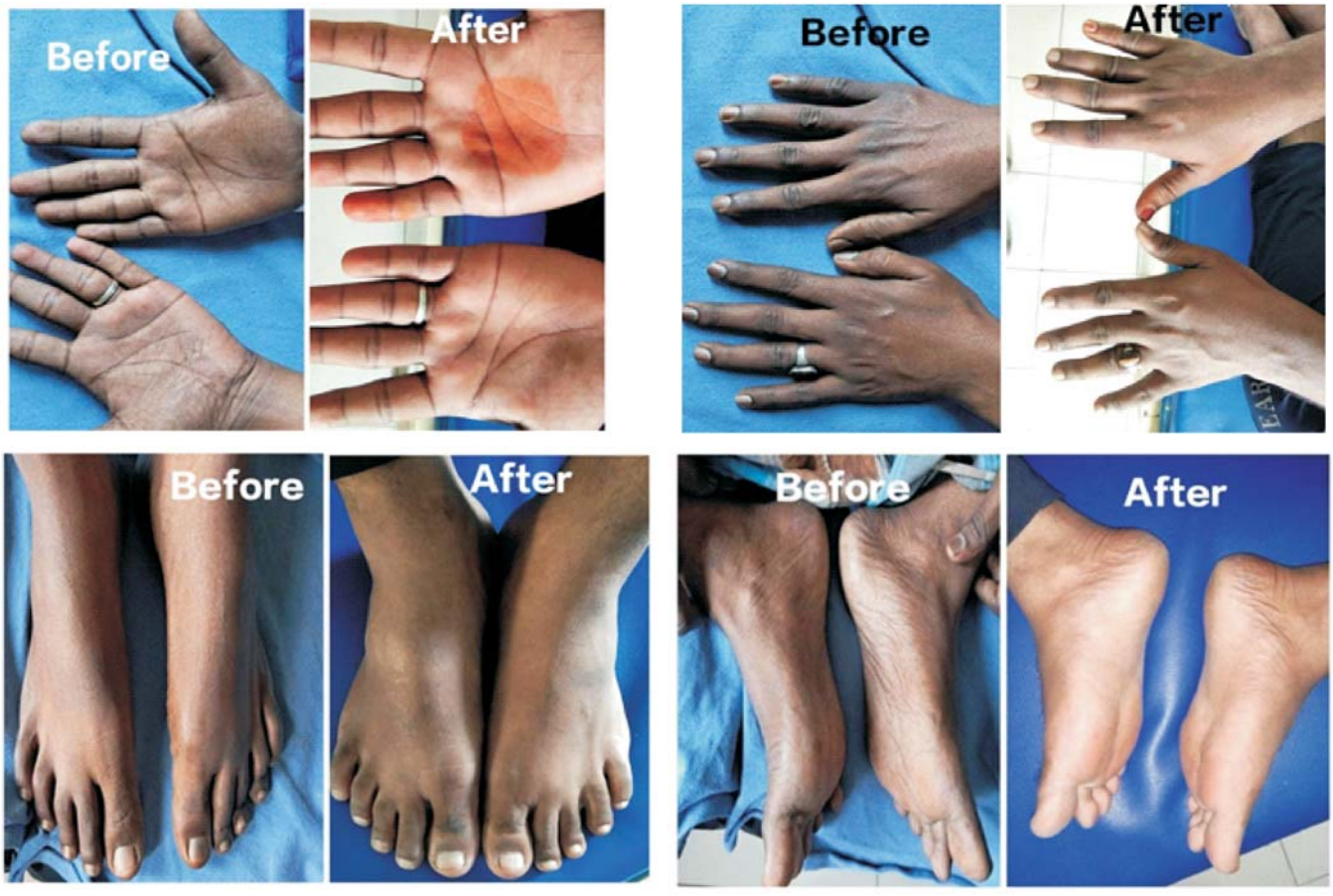
	Labaratory Parameter	Reference Range	Method	29/03/ 2023	02/04/ 2023	03/04/ 2023	04/04/ 2023
1	**Fasting Plasma Glucose**	70-100 mg/dl	hexokinase				102 mg/dl
2	**Random Plasma Glucose**	<140 mg/dl	hexokinase	74 mg/dl			
3	**Esr**	0 - 15 (< 50 year male)	westergren method			45 mm/hr	
4	**Urea**	15 - 43 mg/dl	GLDH, kinetic assay	87 mg/dl	41 mg/dl	42 mg/dl	
5	**Creatinine**	0.72 - 1.25 mg/dl	kinetic	1.99 mg/dl	1.26 mg/dl	1.06 mg/dl	
6	**Sodium** mmol/L	130- 145 mmol/L	Indirect ISE	120.8 mmol/L	127.4 mmol/L	131.5 mmol/L	
7	**Potassium**	3.0- 5.0 mmol/L	Indirect ISE	5.2 mmol/L	5.3 mmol/L	5.52–4.56 mmol/L	
8	**Chloride**	98 – 107 mmol/L	Indirect ISE	93 mmol/L		106 mmol/L	
9	**Calcium**	8.8 -10.6 mg/dl	Arsenazo III	9.7 mg/dl		8.9 mg/dl	
10	**Phosphorus**	2.5 – 4.5 mg/ dl	Phosphom olybdate complex	7.0 mg/dl		4.0 mg/dl	
11	**Hemoglobin**	13- 17 gm%	analyzer	11.8 gm%			
12	**Total Wbc Count**	4 – 11 * 10^3/µL	analyzer	9.8 * 10^3/µL			
13	**Differential Count (N, L, M, E, B)**	40-75% 20-40%, 2-10%, 1-6%, 0-1%	analyzer	47.5%, 36.2%, 4.9%, 10.4%, 1.0%			
14	**Vit B 12**	180- 914 pg/ ml	CLIA		894 pg/ ml		



Photographs showing before and after treatment of the case of Primary adrenal insufficiency.

DISCUSSION

In developed countries the most common cause is Autoimmune Adrenalitis (Isolated -30–40% or as part of autoimmune polyglandular syndromes (APSs) - 60–70%). Infectious diseases are the most common cause worldwide, includes tuberculosis, fungal infections (histoplasmosis, cryptococcosis), and cytomegalovirus infection, HIV etc. Genetic causes are Adrenal hypoplasia congenita (AHC), Adrenoleukodystrophy (ALD) etc. Some rarer causes are drug induced-ketoconazole or rifampicin etc ; and destruction of the adrenal glands as a consequence of infection, hemorrhage(Meningococcal Infection, Primary Antiphospholipid Syndrome) or infiltration (metastasis, lymphoma, hemochromatosis) etc[5].

Symptoms are Weakness, tiredness, fatigue ,anorexia, gastrointestinal symptoms, nausea, vomiting, constipation, abdominal pain, diarrhea, salt craving, postural dizziness, muscle or joint pains. Signs include weight loss, hyperpigmentation (caused by excess ACTH stimulation of melanocytes, most pronounced in skin areas exposed to increased friction, shear stress and sunlight),hypotension. And in women dry and itchy skin, loss of libido, loss of axillary and pubic hair is seen.[2] Chronic adrenal insufficiency manifests with relatively nonspecific signs and symptoms, such as fatigue and loss of energy, often misdiagnosed (e.g., as depression or anorexia). Adrenal insufficiency may mimic features of acute abdomen ,postural hypotension and neurologic disease(decreased responsiveness progressing to stupor and coma)[4]. Hyponatremia, hyperkalemia, elevated blood urea concentration, reversible abnormalities in liver transaminases. low or normal free thyroxine, moderately elevated TSH. Mineralocorticoid deficiency is manifested by elevated plasma renin activity and either low or low-normal plasma aldosterone. Basal plasma cortisol and urinary free cortisol levels are often in the low-normal range

and cannot be used to exclude the diagnosis.[2] The diagnosis of adrenal insufficiency is established by the Short Cosyntropin Test, with excellent predictive diagnostic value, measurement of plasma ACTH is the next step in evaluation. Other Tests- Autoantibodies to 21-hydroxylase, CT scan (enlarged or calcified adrenals, suggesting an infective, hemorrhagic, or malignant diagnosis), CT-guided adrenal biopsy, circulating levels of VLCFA for Adrenoleukodystrophy in men. Chest radiography, tuberculin testing, and early-morning urine samples cultured for Mycobacterium Tuberculosis[5].

Acute adrenal insufficiency is a life-threatening emergency, and treatment with hydrocortisone should not be delayed while waiting for definitive proof of diagnosis. Saline and dextrose therapy will depend on biochemical monitoring and the patient's condition along with treatment of any associated condition (e.g., infection). Clinical improvement, especially in the blood pressure, should be seen within 4 to 6 hours.[5] Long-Term Replacement Therapy of hydrocortisone aims to mimic the normal cortisol secretion rate. Mineralocorticoid replacement is usually also required in the form of fludrocortisones 0.05 to 0.2 mg/day. Decisions regarding doses of replacement therapy are largely based on weight, well-being ,serum electrolytes, supine and erect blood pressures, and plasma renin activity. For women adrenal androgen replacement therapy with 25 to 50 mg/day of DHEA is beneficial.[4]

Conclusion :

Early recognition and prompt management of adrenal insufficiency especially Addison crisis is important as it will prevent patient mortality. Patient education is the key to successful management. Despite treatment, however, patients carry a significant burden of metabolic and psychological comorbidities.[5]

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Case Report

A CASE OF BABINSKI-NAGEOTTE SYNDROME : A SERENDIPITOUS ASSOCIATION OF HYPERHOMOCYSTENEMIA WITH INTRA-ATRIAL THROMBOSIS

Dr. Tony Mathew Austin[1], Dr. Jayashree Sahu[2], Dr. Sagnika Tripathy[3]

Introduction

Firstly diagnosed in 1902, Babinski-Nageotte Syndrome (BNS) is one of the brainstem syndromes characterized by medial as well as lateral medulla oblongata ischemia. In BNS, which has been described in very few cases in the literature, lateral medullary syndrome symptoms as well as contra lateral motor deficit have been observed.

Hyperhomocystenemia, as the name suggests is characterized by increased serum levels of homocysteine, which may have contributory effect on thrombosis, coronary artery disease, stroke, peripheral vascular disease, etcetera. It is amongst a multitude of causatives for stroke in young.

Here, we report a case of BNS in a young female, secondary to Intra-atrial thrombus with underlying hyperhomocystenemia, a rare and serendipitous association,complicated with aspiration pneumonia.

Case Report :

A 34 year old female admitted following an episode of head reeling and sudden loss of consciousness, progressing into hoarseness of voice, difficulty in swallowing and swaying on walking, and recurrent hiccups over 24 hours of onset. On examination, she was conscious, oriented and afebrile with a pulse rate of 72/min, blood pressure of 120/80 mm Hg in right arm in supine position and a respiratory rate of 32/minute. Her head was tilted and rotated to the right side. She had ptosis over right side, increasing on upgaze, miosis of right pupil, bilateral grade II Nystagmus with fast component to right side,with normal light reflexes and extraocular movements. Her uvula was deviated to left side, palatal movements were decreased on right side, gag reflex was absent, had pooling of oral secretions, with absent taste sensation from the posterior 1/3rd of tongue. There was also drooping of shoulder. Apart from diminished pain and temperature sensations over right jaw, cheek and over left upper and lower limbs, all other modalities of sensations were normal. Power over her left upper and lower limbs were decreased to 3/5, with a normal 5/5 power over right upper and lower limbs, with deep tendon reflexes of left side decreased in comparison to the right side. Her cilio-spinal reflex over right side was absent. She also had truncal ataxia with swaying gait to her right, an abnormal finger-nose and finger-nose-finger test, dysdiadokokinesia, rebound phenomenon and heel-knee test over right side.

Examination of other systems revealed soft S1 with a pansystolic murmur in the apical area, decreased breath sounds in her right infra-axillary, infra-scapular and interscapular areas with coarse crepitations.

Her initial NCCT brain revealed no evidence of any bleed, with a hypo-dense lesion over right medulla.

Following the diagnosis of CVA with localization to medulla, the patient was started on oral anti-platelet therapy, with antibiotics and Ryles tube feeding in view of aspiration pneumonia.

Trans-thoracic 2D Echo revealed a thrombus in the left atrium, attached to the inter-atrial septum and plunging into the mitral valvular opening during atrial contraction. MRI of her brain revealed a hyper-intense lesion on T2 and FLAIR, over right medulla, extending into right dorsal cerebellum.

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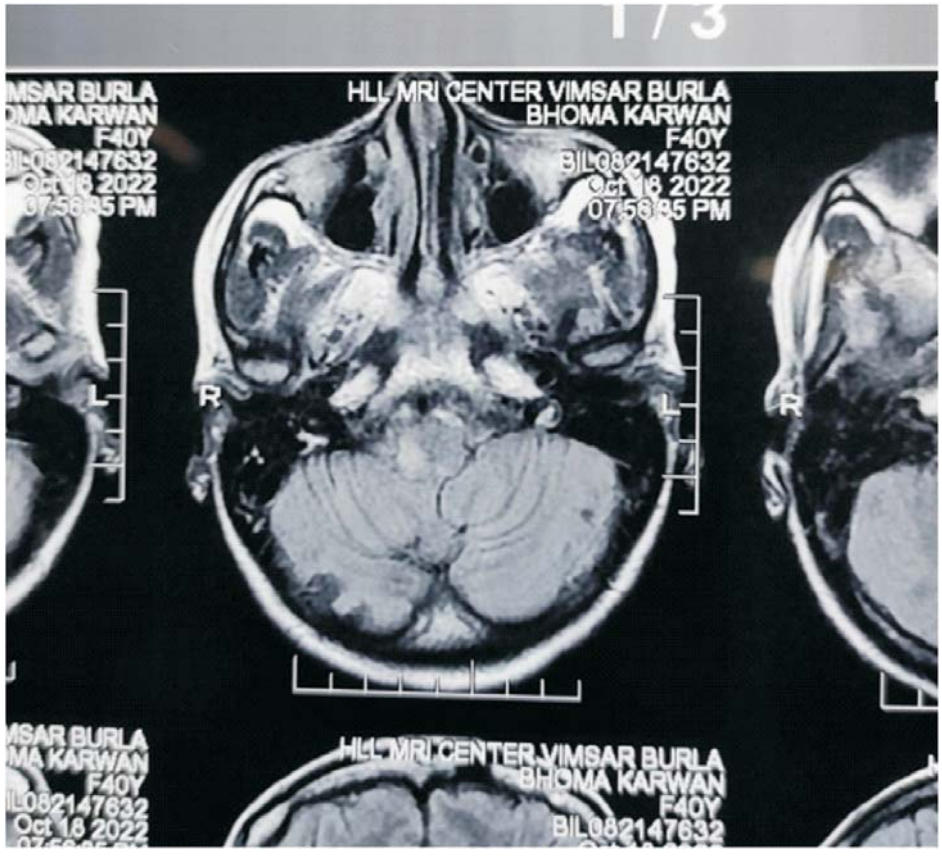
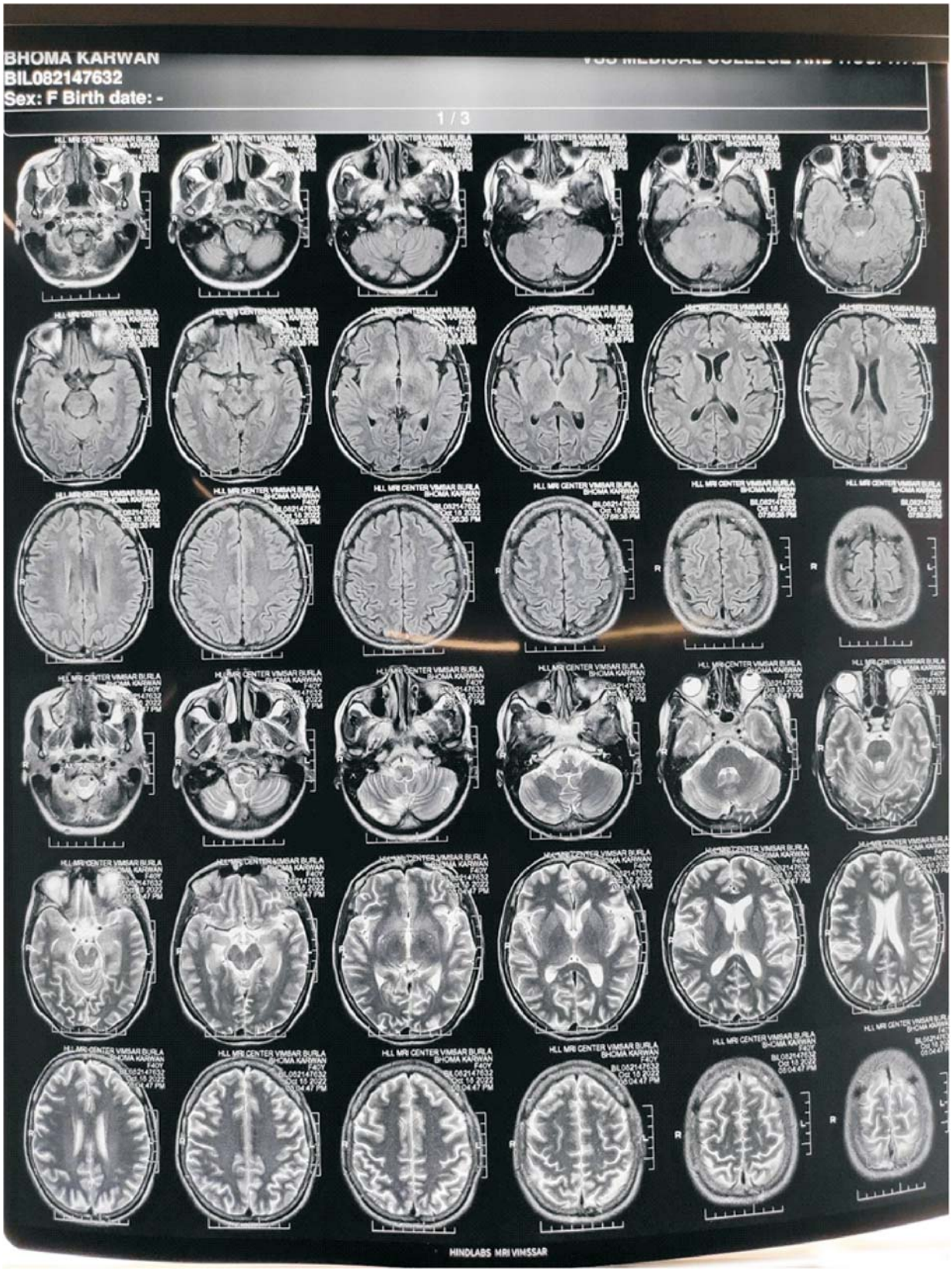
Following the evaluation of stroke possibly secondary to a cardiac embolus, patient was further evaluated, and was found to have elevated levels of serum homocysteine.The patient was hence started on vitamin B6, B12 and folic acid, along with oral nicoumalone. Following the resolution of her pneumonia, she was discharged on the above mentioned vitamins, alongwith clopdiogrel and statin.

Investigations

Haemoglobin	12 g/dl
WBC	12125/mm3
Platelet	210000/mm3
ESR	10mm
S. Urea	25 mg/dl
S. Creatinine	0.8 mg/dl
Totalbilirubin	0.9 mg/dl
DirectBilirubin	0.2 mg/dl
AST	25 IU/L
ALT	21 IU/L
ALP	78 IU/L
S. Sodium	140 mEq/L
S. Potassium	4.2 mEq/L
2D Echo	Thrombus in the left atrium, attached to the inter atrial septum
Non-Contrast CT Brain	Ahypo-denselesion over Right Medulla
MRI Brain	Ahyper intenselesionon T2 and FLAIR, over Right Medulla, extending into right dorsal cerebellum.
S. Homocysteine	64mcmol L(normal<15)
INR	1.1

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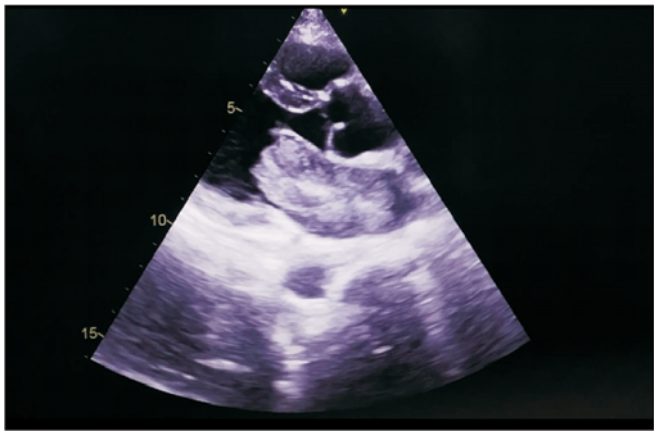

Discussion :

Babinski-Nageotte Syndrome(BNS) is a brain stem syndrome characterized by classical Wallenberg findings alongside muscle weakness of opposite side of thebody,duetoa spreading of the "Wallenbergian" lateral lesion to the pyramidal tract. These classical findings include contra-lateral loss of pain and temperature sensation, ipsilateral facial loss of pain and temperature, dysphagia, dysphonia, impaired gag reflex, vertigo, diplopia, nystagmus, vomiting, ipsilateral Horner's syndrome, ataxia and hiccups.

Despite the developments in recent years in imaging methods,it has been observed that BNS has been still rarely reported. Next to lateral medullary syndrome, the closest differential is hemi-medullary syndrome of Reinhold. Lateral and medial medullar regions are involved in medulla oblongata in hemi-medullary syndrome where as the involvement is limited to lateral medullar zone and corticospinal tract in BNS. The hypoglossal palsy is one of the major differences in the differential diagnosis of hemi-medullary syndrome and BNS. The Cestan- Chenais syndrome, another close differential, includes all symptoms of the Babinski-Nageotte syndrome with the exception of the ipsilateral cerebellar hemi-ataxia because of sparing of the posterior spinocerebellar tract.

The aetiology for BNS includes atherosclerotic occlusions of the vertebral artery followed by Posterior Inferior cerebellar Artery (PICA) as well as pathologies such as syphilitic endarteritis, vertebral artery dissection.

Treatment is dependent on aetiology and involves focusing on relief of symptoms and active rehabilitation to help patients return to their daily activities. In severe cases, a may need to be inserted through the mouth if swallowing is impaired. Long-term treatment generally involves the use of Anti-platelets like aspirin or clopidogrel and statin regimen for secondary prevention. Many individuals will have residual symptoms due to the severity of the blockage as well as the location of the infarction. The outcome may vary among individuals due to but not limited to the size, the location and the aetiology of infarct, and how much damage resulted from it.

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Case Report

ADULT DIABETIC KETOACIDOSIS : ARE WE MISSING LATENT AUTOIMMUNE DIABETES IN ADULTS (LADA)?

Dr. Dhurjati Prasad Mahapatra[1], Dr. Bishnu Prasad Chinhara[2], Dr. Kali Kinkar Chand[3], Dr. Sanjay Kumar Jangid[4]

Abstract

Latent Autoimmune Diabetes in Adults (LADA), a frequently under-diagnosed condition with characteristics of both Type 1 and Type 2 diabetes, usually advances to insulin dependency within 6-12 months due to unresponsiveness to oral hypoglycemic agents (OHAs). Inadequate insulin management can result in emergency admissions with symptoms including dizziness, altered sensorium, and general weakness. This case series at Hi-Tech Medical College and Hospital, Bhubaneswar, from June to December 2023, screened for LADA using GAD65 antibodies and fasting C-peptide assays, emphasizing the importance of early diagnosis and management, particularly in patients unresponsive to multiple OHAs and requiring early insulin. Regular monitoring, adherence to insulin therapy, and periodic reviews are essential to prevent complications such as diabetic ketoacidosis (DKA) and acute kidney injury (AKI). Prompt detection and appropriate management of LADA can substantially improve patient outcomes and decrease emergency hospitalizations.

Introduction :

Latent Autoimmune Diabetes in Adults (LADA) is a frequently misdiagnosed variant of diabetes that exhibits characteristics of both Type 1 and Type 2 diabetes mellitus (DM). Individuals with LADA typically demonstrate a limited response to oral hypoglycaemic agents (OHAs), often necessitating the initiation of insulin therapy within 6 to 12 months of initial diagnosis. However, the management of insulin therapy can be challenging, with issues such as irregular dosing schedules, insufficient doses, omitted doses, or inconsistent adherence. These complications frequently result in patients seeking emergency care, presenting with symptoms including dizziness, altered mental state, and generalised weakness. The lack of recognition of LADA contributes to its delayed diagnosis and suboptimal management. Considering its similarities with Type 1 and Type 2 DM, it is imperative to increase awareness of LADA amongst healthcare professionals to ensure timely diagnosis and appropriate treatment, thereby preventing complications arising from inadequate insulin regulation. The objective of this case series is to facilitate the early screening and diagnosis of Latent Autoimmune Diabetes in Adults (LADA) through the utilisation of diagnostic markers such as GAD65 antibodies and Fasting C-Peptide Assay. This proactive approach aims to reduce the likelihood of LADA patients presenting in emergency settings due to poorly controlled blood glucose levels.

Methods :

This case series was conducted in the Postgraduate Department of General Medicine at Hi-Tech Medical College and Hospital, Bhubaneswar, from June 2023 to December 2023. Patients with diabetes mellitus admitted with clinical suspicion of Latent Autoimmune Diabetes in Adults (LADA) were evaluated based on their presenting symptoms. Established protocols derived from standard prevalent guidelines were adhered to for patient management. Fasting C-Peptide and GAD-65 antibody tests were performed for all patients, and those exhibiting positive results for both markers were included in the case series.

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Case Presentation :

Case 1: A 44-year-old male with a two-year history of diabetes mellitus (DM) on OHAs presented with vertigo, generalised weakness, and altered sensorium. The patient had comorbid hypothyroidism. Upon evaluation, the patient was found to have hyponatraemia, metabolic acidosis, acute kidney injury (AKI), and was treated in the line of diabetic ketoacidosis (DKA) and recovered gradually.Laboratory investigations revealed an HbA1c of 11.5%, fasting C-peptide of 0.01 ng/ml, and GAD-65 antibody levels of 280 IU/ml.

Case 2: A 33-year-old male with a two-year history of DM on multiple OHAs presented with generalised weakness, nausea, and abdominal pain. The patient was a known hypertensive on medication. Upon evaluation was diagnosed with DKA, was treated for the same and improved.His HbA1c was 11.2%, fasting C-peptide was 0.24 ng/ml, and GAD-65 antibody levels were 40.6 IU/ml.

Case 3: A 31-year-old male with a 4-year history of DM presented with generalised weakness and vertigo. Inspite of being on multiple OHAs his previous reports revealed that his sugar levels were uncontrolled since last one year. The patient had no known comorbidities. Upon clinical evaluation, he was diagnosed with DKA, UTI and AKI. His HbA1c was 10.9%, fasting C-peptide was 0.09 ng/ml, and GAD-65 antibody levels were 1365 IU/ml.

Case 4: A 23-year-old female with a 1-year history of DM presented with generalised weakness, nausea, and vomiting. She was well controlled for first few months on metformin and glimiperide. But since last two to three months her sugar levels were high as suggested by her previous health records. Her HbA1c was 13.2%, fasting C-peptide was 0.49 ng/ml, and GAD-65 antibody levels were 2000 IU/ml. The patient on presentation had severe dehydration with high sugar levels and metabolic acidosis. Was treated for DKA and recovered.

All the four cases were discharged on Insulin therapy and on follow up were doing well. Only one case (Case 3) was readmitted for DKA after 3months, as he had stopped insulin and was put on OHAs by his local physician.

Case	Age	Sex	DM Since	HbA1C	Fasting C-Peptide (0.78-5.19ng/ml)	GAD-65 antibody (<17 IU/ml)	Comorbidity	Presenting Features
1	44 Years	Male	2 Years	11.5%	001ng/ml	280IU/ml		Hypothyroid Head reeling, generalized weakness, altered sensorium.On Evaluation Hyponatraemia+ Hypothyroidism+ Metaboilc Acidosis + AKI(?)+DKA
2	33 Years	Male	2 Years	11.2%	0.24ng/ml	40.6 IU/ml		Hypertension Generalised weakness, nausea, pain abdomen.On Evaluation- Hypertension +DKA

3	31 Years	Male	4 Years	10.9%	0.09ng/ml	1365 IU/ml	Nil	Generalised weakness, head reeling.On Evaluation - Hypokalemia+ DKA+ UTI +AKI(?)
4	23 Years	Female	1Year	13.2%	0.49ng/ml	2000 IU/ml	Nil	Generalized weakness, nausea with vomiting.On Evaluation Hypotension+ DKA(?)

TABLE -1 :Comparative analysis of the four LADA cases.

Discussion :

The four cases present with similar predominant characteristics of Latent Autoimmune Diabetes in Adults (LADA) but differ in age, comorbidities, and presenting symptoms. All cases exhibited elevated HbA1c levels (>10%), indicative of inadequate and inconsistent glycaemic control, and tested positive for GAD-65 antibodies, confirming the autoimmune aetiology of LADA. The patients, aged 23 to 44 years, demonstrate that LADA can manifest across a broad adult age range, although it is more frequently diagnosed in younger adults. The variation in diabetes duration (1 to 4 years) indicates differences in disease progression and the rate at which insulin dependence develops. Comorbidities, such as hypothyroidism and hypertension, were present in two cases, emphasising the frequent association of LADA with other autoimmune or metabolic conditions and the necessity for a comprehensive management approach. Presenting symptoms across all cases included generalised weakness and gastrointestinal complaints (nausea, vomiting, pain abdomen), with all patients developing diabetic ketoacidosis (DKA), suggesting that delayed diagnosis or inadequate management can result in severe metabolic complications. Furthermore, two patients experienced acute kidney injury (AKI), delineating the importance of monitoring renal function in LADA patients to prevent further complications.

Latent Autoimmune Diabetes in Adults (LADA) exhibits characteristics of both type 1 diabetes (autoimmune â-cell destruction) and type 2 diabetes (adult onset with initial response to oral hypoglycaemic agents). The presented cases are consistent with these characteristics. Autoimmune â-cell destruction results in insulin deficiency in LADA; however, its gradual progression and non-responsiveness to oral hypoglycaemicdrugs make its diagnosis a challenging affair. Diagnosis in these patients was confirmed utilising GAD65 antibodies and fasting C-peptide assays from standardised laboratories, consistent with findings by *Carlsson et al.* (2019) and *Brahmkshatriya et al.* (2012). Furthermore, the utilisation of renal-specific probiotic strains to reduce serum urea and attenuate inflammatory mediators in acute kidney injury (AKI) aligns with studies by *Fagundes et al*. (2018).

Conclusion :

The above mentioned cases of Latent Autoimmune Diabetes in Adults (LADA) elucidate the gradual progression of insulin dependence and non-responsiveness to oral hypoglycaemic agents (OHAs) over a period of 1-4 years. Individuals diagnosed with Type 1 or Type 2 diabetes within two years, who exhibit non-responsiveness to at least two OHAs and necessitate insulin therapy, as well as those with concomitant autoimmune or endocrinological conditions (e.g., hypothyroidism) presenting with one or more episodes of DKA or AKI, should undergo evaluation for LADA. It is recommended that such patients be subjected to testing for GAD65 antibodies and fasting C-peptide. These diagnostic tests are efficacious for

screening, particularly in recently diagnosed diabetics who do not respond to multiple OHAs and require early insulin initiation. Regular monitoring, strict adherence to insulin therapy, and periodic review at 3-6 month intervals are crucial in preventing emergency admissions and effectively managing LADA.

Conflict of Interest : The authors declare that no conflict of interest exists and no funding was received for this case series.

Human Ethics : Written and informed consent was obtained from the patients prior to the publication of the case series. The Institutional Ethics Committee of Hi-Tech Medical College and Hospital, Bhubaneswar, Odisha issued a waiver for ethics approval for this case series.

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Case Report

WHEN DUST MEETS DISEASE : A CASE OF SILICOTUBERCULOSIS IN AN OCCUPATIONAL WORKER

Dr. Shubham Jainwar[1], Dr. Soumayan Mondal[2]
Dr. Krishna Padarabinda Tripathy[3], Dr. Pradip Kumar Behera[4]

Introduction :

Silicotuberculosis is a complex occupational disease resulting from the concurrent presence of Silicosis and Tuberculosis (TB). Silicosis arises from prolonged inhalation of crystalline silica, leading to chronic lung inflammation and fibrosis. This increases susceptibility to TB in individuals with silicosis. The risk of developing TB in silicosis patients is 3 to 39 times higher than in the general population, making Silicotuberculosis a serious public health concern in regions where TB is endemic [1-4].

In developing countries such as India, where both TB and industrial exposure to silica are common, Silicotuberculosis places a considerable burden on health systems and workers. Industries such as mining, ceramics and stone cutting expose workers to high levels of silica often without adequate protective measures. This results in delayed diagnosis and treatment due to a lack of regular health monitoring [5]. This report details the case of a 51-year-old male with silicotuberculosis, highlighting the diagnostic and management challenges in individuals with prolonged occupational silica exposure.

Case Presentation :

A 51-year-old male from Baripada, Odisha, presented with worsening shortness of breath over six months, a persistent cough with whitish sputum and unintentional weight loss of 10 kg over two months. There was no history of hemoptysis, fever or chest pain but the patient reported fatigue and dyspnea on exertion limiting him to climbing only two flights of stairs. The patient had worked for 20 years in a sanitary ceramics factory, where his job involved handling and grinding ceramic materials, leading to chronic silica exposure.

Eight years prior to his current presentation, the patient was diagnosed with pulmonary tuberculosis following an abnormal chest X-ray. He had been prescribed anti-tubercular therapy (ATT) but due to financial constraints he discontinued the treatment after three months. During his employment, he worked in poorly ventilated conditions with limited access to protective equipment, further compounding his risk of disease.

Examination revealed pallor and clubbing of the fingers, indicative of chronic lung disease. His vital signs were within normal limits, and auscultation demonstrated bilateral coarse crackles particularly in the infrascapular and interscapular regions. Slightly reduced oxygen saturation was noted, without cyanosis. Initial blood work revealed a mildly elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), suggesting ongoing inflammation. His sputum smear was positive for acid-fast bacilli (AFB), confirming active tuberculosis.

High-resolution computed tomography (HRCT) of the chest demonstrated hyperdense parenchymal opacifications with internal calcifications, consistent with advanced silicosis (Figure 1). Fibrotic changes and nodular opacities were seen in both lungs, and ground-glass opacities suggested active infection [1]. These radiological findings, combined with the patient's history of incomplete TB treatment and prolonged silica

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exposure, strongly pointed to a diagnosis of silicotuberculosis.

Diagnostic Challenges :

Diagnosing silicotuberculosis presents significant challenges due to the overlap of clinical and radiological features between silicosis and TB. Both conditions commonly manifest with chronic cough, dyspnea, and weight loss, making differentiation difficult based on symptoms alone [2]. Radiological findings, such as nodular opacities, fibrosis, and calcifications, can be seen in both conditions, further complicating the diagnostic process. In this case, extensive calcified nodules and fibrotic changes on HRCT (Figure 1) were characteristic of silicosis, while ground-glass opacities and AFB-positive sputum confirmed active TB [1,5].

In regions with high TB prevalence, such as India, healthcare providers must maintain a high index of suspicion for silicotuberculosis in patients with a history of silica exposure, especially when TB treatment has been incomplete. Diagnostic delays are common, particularly in underserved populations where access to advanced diagnostic tools, such as HRCT or bronchoalveolar lavage (BAL), is limited [3]. The combination of the patient's incomplete ATT and continued silica exposure made silicotuberculosis the most likely diagnosis.

Pathophysiology of Silicotuberculosis :

Silicosis occurs when silica particles are inhaled and deposited in the lungs, leading to chronic inflammation and fibrosis. Macrophages, responsible for clearing infections, are overwhelmed by silica particles and become dysfunctional, increasing susceptibility to infections such as TB [2,6].

Silica particles induce a fibrogenic response, leading to the formation of silicotic nodules. Over time, these nodules coalesce, causing progressive lung fibrosis and reduced lung function. Continuous irritation by silica also impairs the immune system's ability to contain latent TB, increasing the likelihood of reactivation. The risk of TB is further elevated in patients with acute or accelerated silicosis, which causes more severe lung damage and immune suppression [3].

In this case, the patient's prolonged silica exposure likely contributed to chronic silicosis, while his incomplete TB treatment allowed the infection to persist and eventually reactivate. This interaction between silica-induced lung damage and TB reactivation is characteristic of silicotuberculosis and requires careful diagnostic and therapeutic management [4,5].

Management :

The management of silicotuberculosis involves treating both the active TB infection and the underlying silicosis. The patient was initiated on a standard four-drug ATT regimen, including isoniazid, rifampicin, pyrazinamide, and ethambutol. Given the extent of pulmonary fibrosis, the treatment duration was extended beyond the standard six months to ensure effective drug penetration and reduce the risk of treatment failure [4,5].

Supportive care was provided to manage the patient's respiratory symptoms and improve lung function. Bronchodilators were prescribed to relieve dyspnea, and mucolytics were administered to assist with sputum clearance. Nutritional support was provided to address the patient's weight loss, and physiotherapy was recommended to maintain lung function.

The patient was also counselled on the need to avoid further silica exposure, as continued exposure would exacerbate his condition and increase the risk of TB recurrence. He was advised to seek alternative employment or use appropriate personal protective equipment (PPE), such as respirators, if exposure to dusty environments was unavoidable [6].

Long-term Management and Prognosis :

The prognosis for patients with silicotuberculosis is often poor, particularly in those with advanced silicosis. Although ATT can successfully treat the TB infection, the lung damage caused by silicosis is irreversible. Patients with silicosis are at increased risk of chronic respiratory failure, cor pulmonale, and chronic obstructive pulmonary disease (COPD) [1,5].

In this case, the extensive fibrosis and calcified nodules observed on HRCT suggest an advanced stage of silicosis, likely requiring long-term monitoring and supportive care. While sputum conversion to AFB-negative status was achieved after two months of treatment, the patient will require ongoing follow-up to monitor for TB recurrence and progression of silicosis. Pulmonary rehabilitation and long-term oxygen therapy may be necessary as the disease progresses [6].

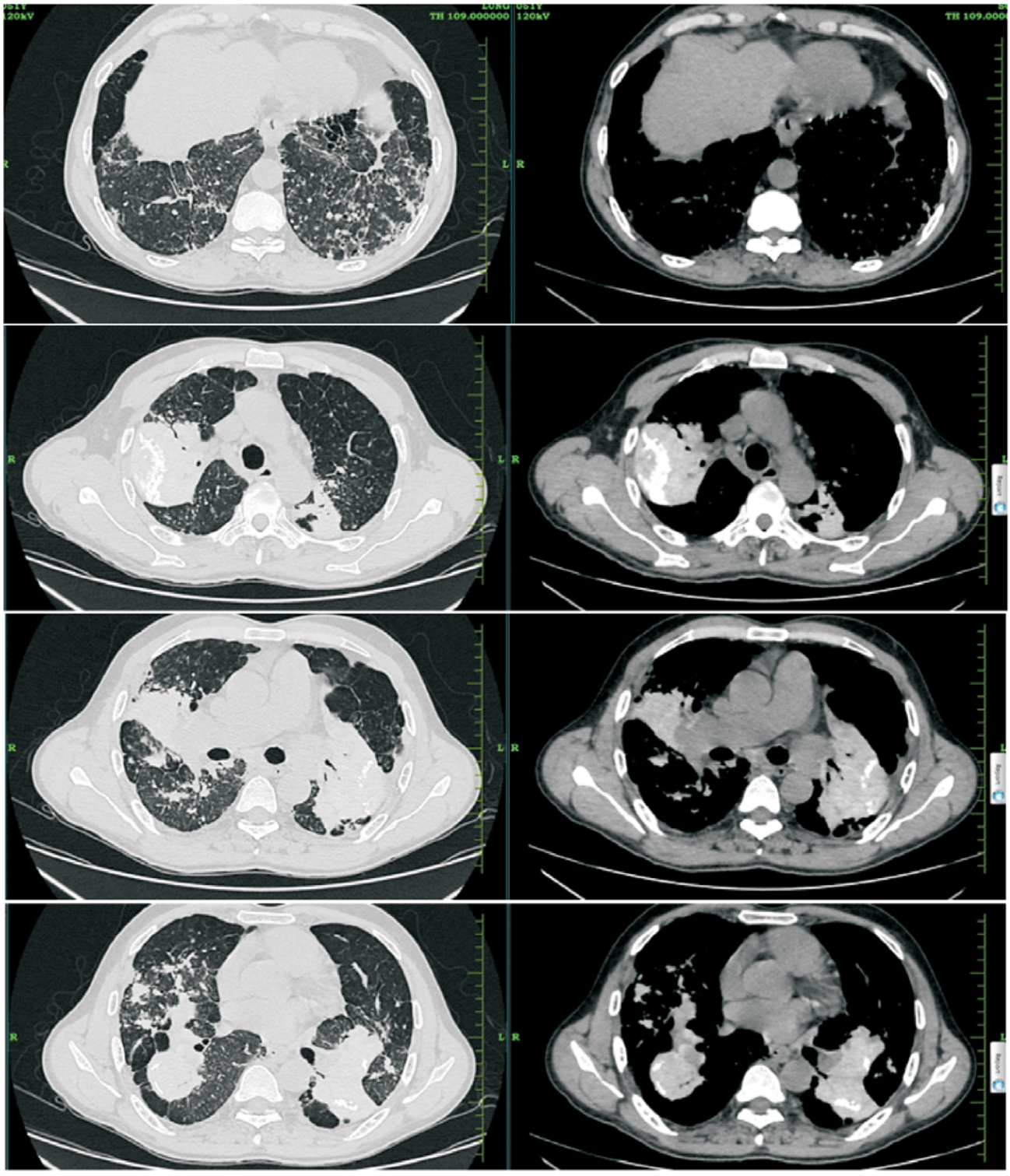

Figure 1 : HRCT chest showing extensive hyperdense parenchymal opacifications with patchy internal calcifications, consistent with progressive massive fibrosis secondary to silicosis. Surrounding fibrotic changes are observed bilaterally. Ground-glass opacities and multiple nodular opacities are also present in both lungs, indicative of concurrent active tuberculosis.

Occupational Health Implications:

This case emphasizes the critical importance of occupational health measures in preventing silicosis and silicotuberculosis. Workers in industries with high silica exposure should undergo regular health screenings, including chest X-rays and pulmonary function tests, to enable early detection of silicosis. Employers must enforce the consistent use of PPE, such as respirators, and ensure proper workplace ventilation to minimize dust levels [5].

In India, where both TB and silica exposure are prevalent, integrated occupational health programs combining TB screening with silicosis prevention measures are essential. Public health interventions, including education on the risks of silica exposure and the importance of completing TB treatment, can significantly reduce the incidence of silicotuberculosis [2,5].

Conclusion:

This case report of silicotuberculosis in a former sanitary ceramics worker highlights the serious health risks posed by prolonged occupational exposure to silica. The diagnostic and therapeutic challenges of this dual pathology underscore the need for early recognition, complete ATT, and supportive care in managing silicosis. Multidisciplinary management, early detection, and adherence to treatment protocols are critical to improving outcomes for patients with silicotuberculosis, particularly in resource-limited settings. Preventative occupational health strategies, such as the use of PPE, regular health screenings, and public health interventions, are vital in reducing the burden of silicotuberculosis in high-risk industries and TB-endemic regions [1,6].

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Case Report

REVERSIBLE MEMORY LOSS IN A CASE OF MEGALOBLASTIC ANAEMIA : A CASE REPORT

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Abstract :

Vitamin B12 is an essential component for haematological and neurological function in our body. Its deficiency is associated with severe macrocytic anaemia and neuropsychiatric manifestations. We report a case of a 34 years old, male patient presenting with features of severe anaemia and rapidly progressive memory loss. Complete blood analysis indicated severe magaloblastic anaemia and peripheral smear was suggestive of macrocytic picture. Metabolic workup showed decreased Vitamin B12 levels. All other routine blood tests were within the normal range. Radiological imaging confirmed demyelinating lesions in the spinal cord. Intramuscular injection of methylcobalamin was started and the patient improved gradually.

Key Words : Vitamin B12, Macrocytic anaemia, Sub-acute combined degeneration of spinal cord, Neuropsychiatric disorder

Introduction :

In developing countries, Vitamin B12 deficiency is one of the common causes of nutritional anaemia, predominantly in individuals on vegetarian diet. It can lead to neuropsychiatric manifestations such as peripheral neuropathy, cerebellar ataxia, cognitive deficits, psychosis, mood disorders and dermatological manifestations like hyperpigmentation. Herein we present a case of Vitamin B12 deficiency anaemia with neurological manifestations, which after careful evaluation, was diagnosed as a case of sub-acute combined degeneration of spinal cord.

Case Report :

A 34 years old, male patient presented to our hospital with complaints of tingling of extremities, progressive swelling of both feet, shortness of breath on exertion and generalised weakness for 8 months, followed by difficulty in walking and tendency to fall while walking since last 2 months. During the same period, he also experienced cognitive decline in the form of impaired memory and forgetfulness. There were no known co-morbidities. The patient has history of blood transfusion of 3 units of packed cell about 8 months back. He takes mostly vegetarian diet, has normal bowel and bladder habits, no addiction and belongs to low socio-economic class.

On general examination, patient was conscious and cooperative .There was severe degree of pallor with hyperpigmentation of skin, mostly in periungual areas and palms and bilateral pitting pedal edema.

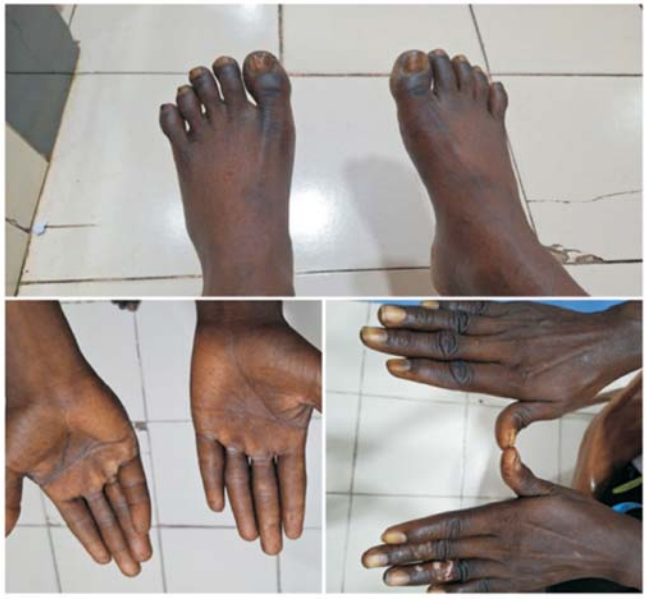

Figure 1: Showing hyperpigmentation in periungual areas and palms.

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On neurological examination, his higher mental functions were impaired in the form of cognitive deficits particularly immediate and recent memory loss. All cranial nerves were intact. On examination of the motor system, the bulk, power, tone and reflexes were normal in the both upper limbs. In the lower limbs, although muscle bulk was normal but the power was 4/5 bilaterally in all group of muscles. In both the legs, the knee jerk was absent but ankle jerk was present bilaterally i.e, Westphal's sign was positive. Plantar reflex was extensor on both sides i.e positive Babinski's sign. The vibration sense and proprioception was impaired in both the lower limbs. Cerebellar signs were positive in the form of abnormal finger-to-nose test, dysdiadochokinesia and abnormal shin-to-heel test. The patient had tendency to fall on standing and Romberg's sign was positive. The gait was ataxic.

Initial laboratory investigations indicated haemoglobin level of 4.5 gm/dl and MCV- 117.5 fl. Total leukocyte count, total platelet count, liver function test , renal function test, urine analysis and iron profile were within normal range. Peripheral smear was suggestive of macrocytic anaemia and presence of hypersegmented neutrophils. Stool occult blood test was negative. Serum vitamin B12 was 97 pg/ml (normal range: 180-914 pg/ml), Serum homocysteine was 16.65 micromol/l (normal range: 5.2-11.4 micromol/l). Chest X-ray, Ultrasound of abdomen and pelvis, UGI Endoscopy, 2DECHO, MRI of brain and NCS of both upper and lower limbs revealed no significant abnormality. MRI of spine indicated demyelinating lesions in the form of symmetrical bilateral T2 hyperintensities in the dorsal column of spinal cord from C7 to D11 vertebral levels- likely Sub-acute combined degeneration of spinal cord. Somato-Sensory Evoked Potential study revealed conduction delay in the posterior column fibres of the spinal cord in both cervical and thoracic region.

The patient received 2 units of PRBC transfusion and was started on Inj.Methylcobalamin (1000 mcg) intramuscularly once daily for 7 days, along with other supportive treatment. The gait improved gradually and the haemoglobin level increased to 7.6 gm/dl. The patient was discharged with advice of Inj.Methylcobalamin (500 mcg) intramuscularly once weekly for 4 weeks, followed by intramuscularly once monthly for lifelong. On follow up after 3 months his gait had improved significantly along with constitutional symptoms.

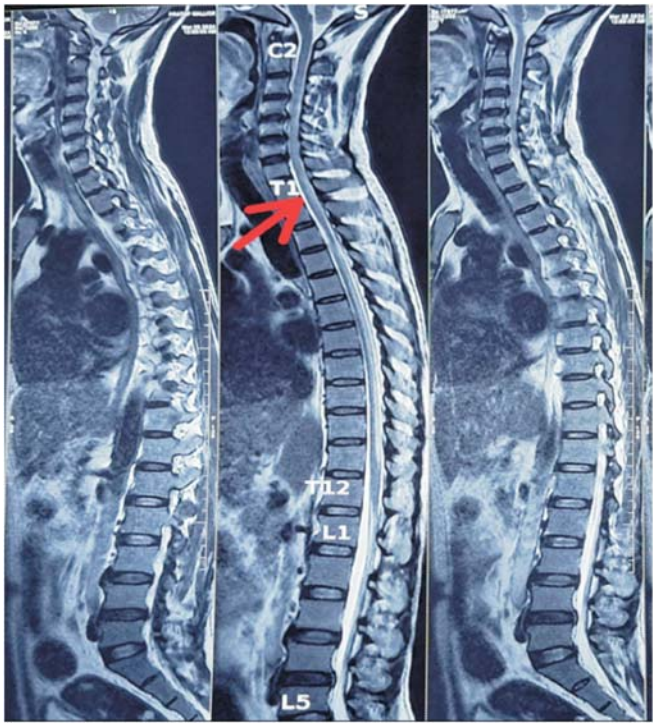

Figure 2: Showing T2 hyperintensities in the dorsal column of spinal cord from C7 to D11 vertebral levels.

Discussion :

Vitamin B12, also called as Cobalamin, is a water soluble vitamin. Poultry, meat, fish and dairy products are its rich sources. Nutritional anaemia is more prevalent in developing countries. Vitamin B12 deficiency is a concern, particularly for those primarily consuming vegetarian/vegan diets. Causes of this deficiency includes decreased intake, malabsorption, pernicious anaemia, post-ileal resection, post-gastrectomy, chronic *H.pylori* infection, infestation with fish tapeworm (*Diphyllobothrium latum)* , alcohol consumption, and chronic use of certain drugs such as proton pump inhibitors, histamine 2 receptor antagonists (H2RA), chloramphenicol, ethanol, colchicines, etc.

Vitamin B12 plays a pivotal role in DNA maturation and myelin stability. [1] It converts homocysteine to methionine, with the by-product being utilised in the synthesis of pyramidine bases of DNA. [1]Due to Vitamin B12 deficiency, there is impaired

synthesis of DNA in the erythroid precursors leading to anaemia. Vitamin B12 also serves as a co-factor for enzymes methyl malonyl CoA mutase, which facilitates conversion of Methyl malonic CoA to Succinyl CoA. This enzymatic defects resulting from Vitamin B12 deficiency leads to accumulation of Methylmalonic acid and Homocysteine, which appears to be proportionally related to the severity of the associated neurological and psychiatric abnormalities. [2]

Sub-acute combined degeneration (SACD) of spinal cord is a classic disease, a metabolic disorder of the spinal cord due to Vitamin B12 deficiency. [3] There is involvement of the dorsal and lateral columns of the spinal cord. The neuropsychiatric manifestations of Vitamin B12 deficiency affect the brain, spinal cord, optic nerve and peripheral nervous system. [4] Symptoms of anaemia usually precede the neurological manifestations. The earliest symptoms and signs are related to the damage to peripheral nerves instead of the spinal cord. [3] This treatable myelopathy presents with subacute paresthesias in hand and feet, loss of vibration & position sense and a progressive spastic & ataxic weakness. [5] The myelopathy of subacute combined degeneration of spinal cord tends to be diffuse rather than focal, signs are generally symmetrical and reflects predominant involvement of posterior and lateral tracts, including Romberg's sign. [5] Other neurological manifestations of Vitamin B12 include behavioural changes, psychosis, dementia, optic nerve involvement, bladder dysfunction, paraparesis and quadriparesis. The diagnosis can be confirmed by presence of megaloblastic anaemia, low serum Vitamin B12 levels along with demyelinating features in the spinal cord in the neuroimaging study. Treatment is by replacement therapy, beginning with 1000 mcg of intramuscular Vitamin B12 injection daily for 5 days and then continued once monthly maintenance dose. [5] Oral maintenance dose is also reasonable, except in cases of pernicious anaemia. [5] For pernicious anaemia, a convenient therapeutic regimen is 1000 mcg of methylcobalamin injection intramuscularly daily for 1 week, then weekly once for 1 month and then monthly once for the remainder of the patient's life. [6] Differential diagnosis of subacute combined degeneration of spinal cord includes recreational abuse of inhaled nitrous oxide, copper deficiency, excessive zinc ingestion, folate deficiency associated myelopathy, tabes dorsalis and transverse myelitis.

Conclusion :

This case highlights the significance of estimation of serum Vitamin B12 in patients presenting with anaemia along with neurological symptoms. Further neuroimaging studies should be done to confirm the diagnosis of sub-acute combined degeneration of spinal cord. Timely diagnosis and treatment with vitamin B12 supplementation results in correction of anaemia as well as marked neurological improvement.

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Case Report

VOCAL CORD PALSY : AN UNUSUAL PRESENTATION IN SYSTEMIC SCLEROSIS

Dr. Saurav Kumar Mallick [1], Dr. S.N. Jali[2]

Abstract :

A 36 years old female presented with hoarseness of voice, difficulty in swallowing, nasal regurgitation, tightness of skin in different parts of the body with discolouration of finger tips. Further investigations revelaed that she is having Systemic sclerosis with Vocal cord palsy which is a very rare presentation.A multidisciplinary approach for appropriate patient management is therefore important.

Introduction :

Systemic sclerosis(SSc) or Scleroderma is an autoimmune disease characterized by chronic inflammation with variable degrees of collagen accumulation (fibrosis)in affected tissues and obliterative vasculopathy of peripheral and visceral vasculature. The skin is most frequently affected resulting in diffuse thickening known as Scleroderma .Vocal cord paralysis seems to be extremely rare in SSc and few cases were reported .Laryngeal inflammation has been attributed to gastro-esophageal reflux, vocal cord thickening ,nodularity or fibrosis while vocal cord palsy has been related to cricoarytenoid ankylosis and nerve injury. This report describe a patient with SSc presented with hoarseness of voice due to unilateral rt vocal cord palsy.

Case Report :

A 36 years old female patient,housewife by occupation, presented with hoarseness of voice and difficulty in swallowing associated with nasal regurgitation of food for 20 days. She also complained of tightness of skin over face,bilateral upper limbs, lower limbs and trunk associated with hypopigmented patches over limbs and facesfor 2-3 years. She also gave the history of hair loss with discolouration of skin around tip of the fingers. No H/O limb weakness,No H/O of fever, weight loss,vomiting,breathlessness. There was past history of bluish discolouration of finger on cold exposure,heartburn and regurgitation of food for more than a year.

On general Examination pt was alert, oriented to time, place and person , Pulse rate-76/min,BP-126/74mmHg,RR-18/min,temp-afebrile, There was tightness of skin over face, upper and lower limbs with Loss of hair from lateral part of eyebrows and Microstomia.There was no cranial nerve deficits; sensory and motor system examination-normal

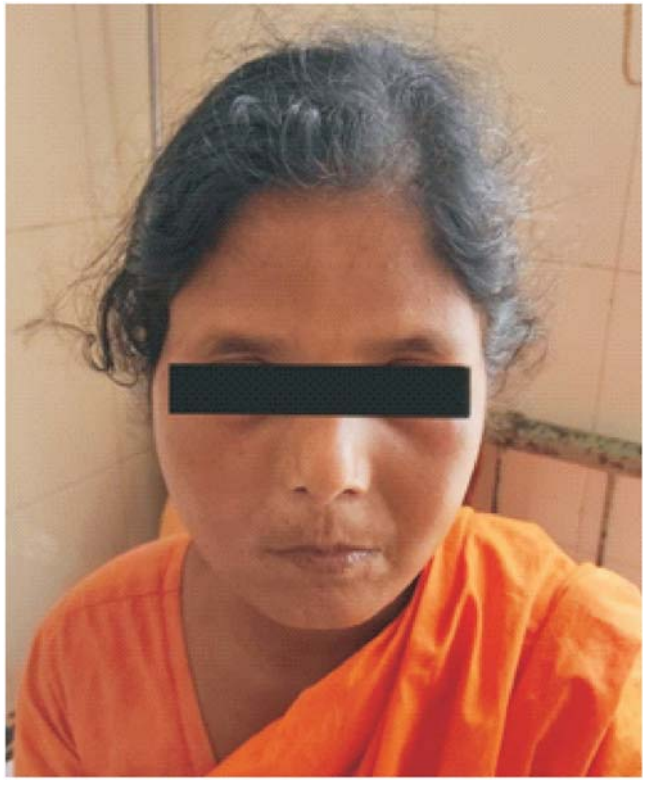

Figure - 1 : Thickening of skin over face with loss of hair from lateral part of eyebrows

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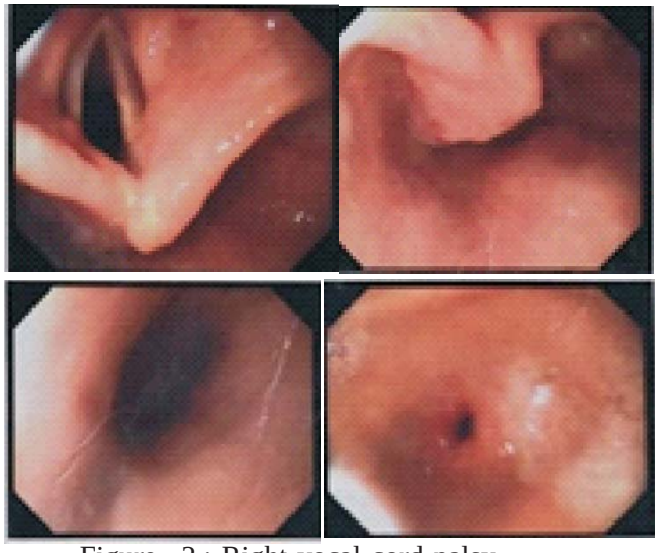

Figure - 2 : Right vocal cord palsy

Laboratory Investigation :

All routine examination like CBC, RFT, LFT, TFT within normal limits. ANA-positive, SCL-70 antibody-strongly positive

Fibro-optic Laryngoscopy revealed - Right immobile vocal fold nearly in the median position and postcricoid oedema and redness.The arytenoid cartilage was firmly fixed in full adduction.

Upper GI endoscopy-right vocal cord palsy, GERD and antral gastritis.

Treatment : Pt was put on low dose tab prednisolone course for 1 month along with tab amlodipine and tab tadalafil to prevent vascular complication. After 1 month follow up pt symptoms slightly improved.

Discussion :

The cricoarytenoid joint is a true synovial joint and, therefore ,is susceptible to local and systemic disease of the synovium .Rheumatoid arthritis is most commonly associated with cricoarytenoid joint involvement. Arthritis is not a common feature of scleroderma; when present in acral joints ,scleroderma -associated arthritis resembles rheumatoid arthritis. The synovium demonstrates an infiltrate of lymphocytes and plasma cells and there is a thick layer of fibrin deposited in the joint space that can eventually lead to fibrous ankylosis. If such fibrous ankylosis occur in the cricoarytenoid joint that can lead to cricoarytenoid joint fixation and vocal cord paralysis.When respiratory distress is present ,emergent tracheotomy may be necessary .If the airway is not in jeopardy ,the arthritis can be treated with anti inflammatory medications such as oral steroids.

Conclusion :

Systemic sclerosis is a multi-system disorders that may affect larynx. Laryngeal involvementis not uncommon in active and progressive clinical course. However ,it can also occur in silent or inactive disease. Not only should general medicine doctors be aware of laryngeal involvement in SSc but also ENT surgeons should be actively involved in the management of the patients. The need for a multidisciplinary approach for appropriate patient management is there fore important.

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Case Report

TUBERCULOSIS MASQUERADING AS NEUROMYELITIS OPTICA : A RARE CASE REPORT

Dr. Surabhi Mishra[1], Dr. Premakanta Mohanty[2], Dr. Soumya Kumar Acharya[3], Dr. Namita Mohapatra[4]

Introduction :

Transverse myelitis (TM) is a focal inflammatory disorder of the spinal cord, often associated with infectious disease, which can lead to permanent paraplegia or quadriplegia. Cases of transverse myelitis associated with TB are very rare or usually not reported.[1] We report a case-patient with TB presenting with optic neuritis and long extended transverse myelitis.

Case Description :

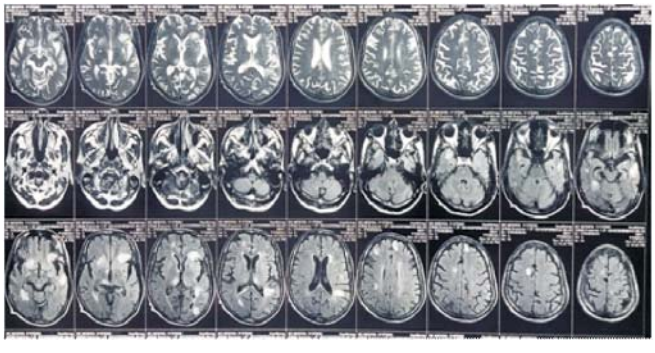
50 yr. old male presented with chief complaints of Pain in lower back radiating to B/l lower limbs and Weakness of both lower limbs associated with tingling and numbness for 3days with Inability to pass urine and stool for 1 day .There was No history of Headache, Seizure, Loose stool, vomiting, significant weight loss, , cough or high risk behaviour, neck pain, trauma to back,difficulty in swallowing , nasal regurgitation, hoarseness of voice, recent vaccination or animal bites. There was Past History of fever associated with cough 2 months back lasting for one and a half month for which he was treated at the local hospital. No h/o any chronic illness or contact with TB patients. The patient had normal vitals at presentation and general-examination revealed no abnormality.

On neurological examination he had normal higher function with visual acuity of 6/24 in right eye and 6/18 in left eye and no improvement with pinhole. Fundoscopy was normal in both eyes. Normal higher function, other cranial nerve functions, motor, sensory, cerebellar and autonomic functions. Other cranial nerve functions were normal. There was normal bulk in all 4 limbs, normal tone and power in B/L upper limbs with hypertonia in B/L lower limbs with a power of 3/5 across all joints in all ranges of motion. B/l plantar extensor, B/L abdominal and cremasteric reflex being absent. DTRs normal in B/L ULs and Exaggerated in B/L lower. Sensory examination, cerebellar and autonomic functions are all within normal limits. Other systemic examinations are within normal limits.

Investigations :

ESR	88 mm/hr (↑)
CRP	55 mg/L (↑)
ANA	Negative
AQP4 ab	Negative
MOG ab	Negative

Parameters	**Value**
Hb	11 g/dl
RFT	WNL
LFT	WNL
FBS	80 mg/dl



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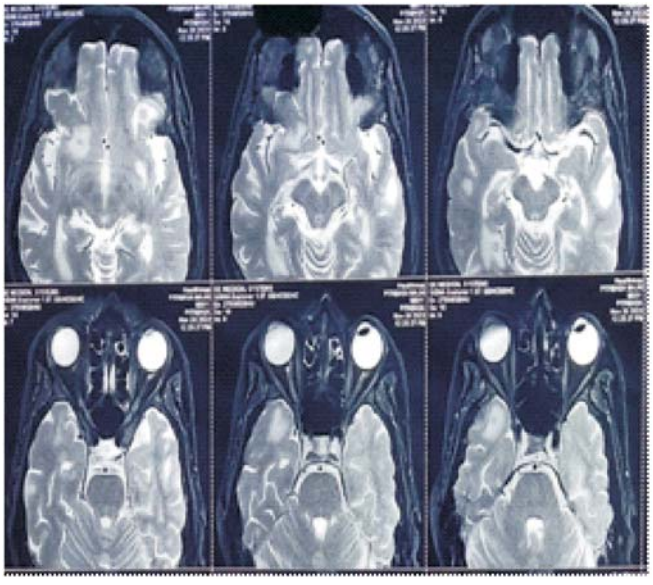
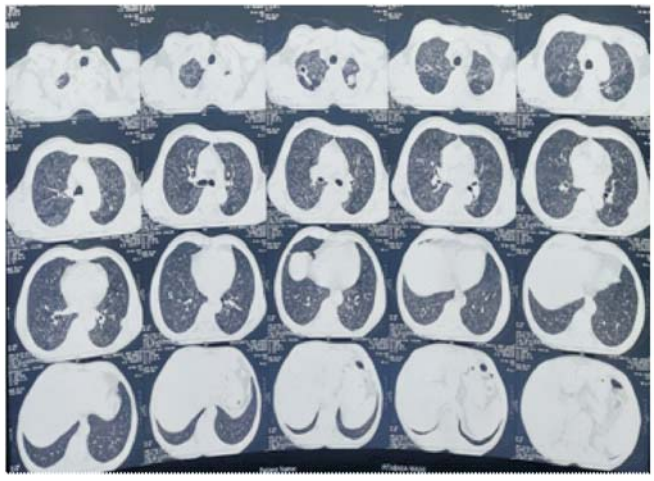


MRI LS Spine with screening of whole spine	Transverse myelitis Long Segment (D5 to conus medullaris) with PIVD changes C3-C6
MRI Orbit	Hyperintensity along bilateral optic nerve (optic neuritis)
MRI Brain	Abnormal T2 FLAIR hypointense nodules surrounded by oedema seen subcortical and deep white matter in bilateral frontotemporopari-etooccipital lobe ? Granulomatous Lesions ? Mets With dilated ventricles

CSF Study	Value
Glucose	52 mg/dl
Protein	180.08 mg (high)
Cells	Paucicellular, \ Lymphocyte predominant with degenerated cells in a proteinaceous background
ADA	4.5 U/l
Malignant cells	Negative
OCB	Absent
Indian Ink preparation	No budding or yeast cell like growth seen
GENEXPERT	MTB detected, Rifampicin sensitive

Chest X-ray	Multiple miliary shadows in B/L lung fields with homogenous opacity of B/L upper zones
HRCT Thorax	Multiple fibro-cavitary lesions seen on bilateral upper lobes. Active lesion of TB Multiple miliary nodules seen in bilateral lung field. Multiple pleural based nodules seen in left side
Sputum AFB CBNAAT	Negative
Broncho-Alveolar Lavage	Pauci-cellular cytology with no malignant cells. CBNAAT negative



Diagnosis :

Long extended transverse Myelitis with B/L Optic Neuritis (Seronegative NMO) in Disseminated Tuberculosis.

Management :

Patient was treated with high dose pulse steroid therapy followed by a tapering dose along with ATT for 9 months. Patient is doing well on follow up.

Conclusion :

Tubercular infection of central nervous system (CNS) is still a major cause of morbidity and mortality in low-to-middle-income countries.[1] Spectrum of CNS-TB include most frequently tubercular meningitis followed by tuberculoma, tubercular abscess, cerebral miliary TB, TB encephalitis and encephalopathy, tubercular arteritis[2] and spinal tuberculosis whereas LETM as a manifestation of spinal TB is extremely rare.[3] Exact pathogenesis of demylination in TB is yet to be elucidated, however, an immune-inflammatory response to the infectious agent or the infection itself has been postulated as a cause in previous literature.[4]

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Case Report

A CASE REPORT OF LOW-DOSE METHOTREXATE TOXICITY LEADING TO PANCYTOPENIA AND SYSTEMIC TOXICITY

Dr. Shibani Biswal[1], Dr. Tuhin Hati[1], Dr. Lagendra Kumar Singh[2], Dr. Shradhanjali Pani[3]

Abstract:

Methotrexate is commonly used in low doses for the treatment of autoimmune diseases. However, even at low doses, it can lead to severe adverse effects, including pancytopenia and systemic toxicity. This report presents a 60-year-old female patient who developed pancytopenia, mucositis, and systemic toxicity after low-dose methotrexate therapy for rheumatoid arthritis. Early identification and prompt discontinuation of methotrexate, along with supportive care, led to the patient's gradual recovery. This case highlights the need for careful monitoring and awareness of the potential toxic effects of methotrexate, even at low doses, in elderly patients.

Introduction :

Methotrexate is widely used in the treatment of rheumatoid arthritis due to its disease modifying potential and generally favorable safety profile at low doses (10-25 mg/week).

However, methotrexate toxicity, particularly pancytopenia, remains a rare but serious complication, especially in older adults with risk factors like renal impairment, hypoalbuminemia, or polypharmacy. In this case report, we describe a patient who developed methotrexate-induced pancytopenia and systemic toxicity. Previous cases reported in the literature have highlighted the need for careful monitoring and early intervention to prevent life-threatening complications.

Case Presentation :

A 60-year-old female, has a known history of rheumatoid arthritis (RA), characterized by significantly elevated RA factor (108.7 IU/ml), CRP (138.5 mg/L), and ESR (111/1st hr). Her disease had been managed with a weekly dose of methotrexate, 15 mg. She presented with general symptoms of malaise, fatigue, and worsening shortness of breath. Laboratory investigations revealed pancytopenia with critically low blood cell counts: WBC at 740/μL (normal range: 4,000–10,000/μL), hemoglobin at 6.5 g/dL (normal range: 12–16g/dL), and platelets at 24,000/μL (normal range: 150,000–450,000/μL). Further clinical evaluation with an upper GI endoscopy showed esophageal candidiasis, gastroesophageal reflux disease (GERD), and varices. Additionally, her clinical presentation included mucosal ulceration, signs of anemia and bleeding tendencies (petechiae) likely due to thrombocytopenia. A diagnosis of pancytopenia secondary to methotrexate toxicity was established. Differential diagnoses such as Felty's syndrome, hemophagocytic lymphohistiocytosis (HLH), and complications related to infections were also considered, but methotrexate toxicity was confirmed due to the clinical presentation and the patient's positive response to leucovorin and filgrastim therapy. Treatment involved the immediate discontinuation of methotrexate and the initiation of leucovorin at 15 mg three times daily to mitigate methotrexate's toxic effects. Supportive care, including blood transfusions and broad-spectrum antibiotics, was provided to manage febrile neutropenia. The patient showed marked improvement within five days and was subsequently discharged.

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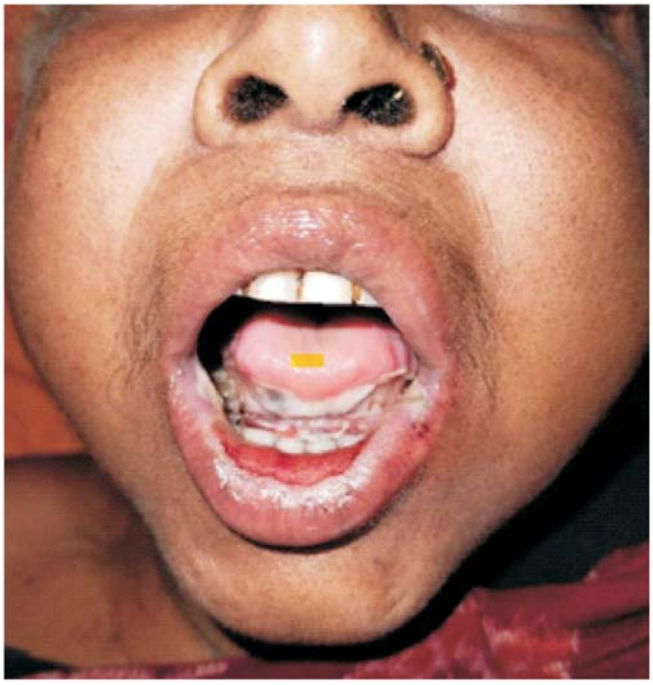

Fig: Mucosal ulceration caused by low-dose methotrexate

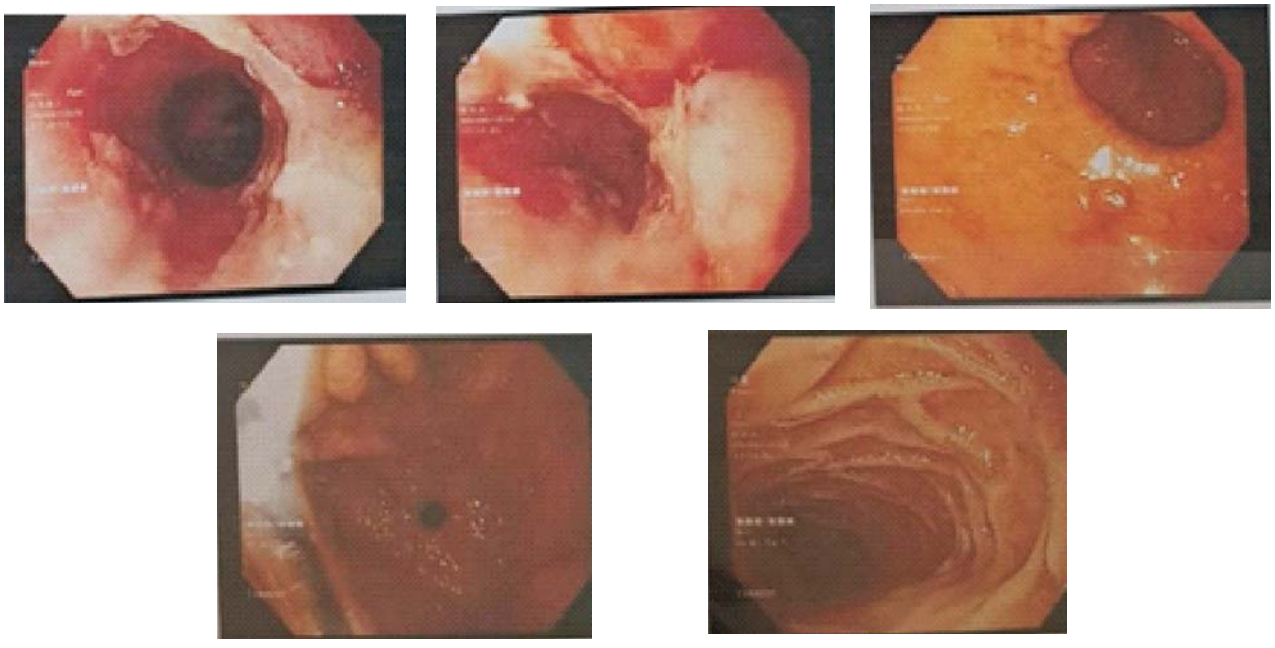

Fig: Upper GI Endoscopy Esophageal candidiasis with varices with GERD

Discussion:

Methotrexate-induced pancytopenia is a serious complication, particularly in patients with underlying comorbidities such as chronic kidney disease, advanced age, or poor nutritional status. Multiple case reports, including one by Kanderi et al., highlight how even low-dose methotrexate can cause fatal pancytopenia in elderly patients with risk factors. In this case age, and comorbidities may have exacerbated the toxic effects of methotrexate. Similar to the case presented by Gonzalez-Ibarra et al., this patient's pancytopenia was managed effectively by discontinuing methotrexate and initiating leucovorin rescue therapy. The case by Gonzalez-Ibarra et al. presented a 73-year-old female who experienced severe neutropenia and mucocutaneous bleeding after being on low-dose methotrexate for rheumatoid arthritis. This highlights that the risk of significant myelosuppression increases with factors like age, renal function, and inadequate monitoring of blood counts following medication adjustments. Frequent monitoring of complete blood count (CBC), renal function, and liver enzymes is essential for patients on methotrexate therapy. The American College of Rheumatology recommends routine blood work every 2-4 weeks during the initial phase of methotrexate treatment, which is crucial for preventing severe outcomes such as pancytopenia.

Conclusion:

Methotrexate-induced pancytopenia, even at low doses, presents a significant risk, especially in older adults with renal impairment or polypharmacy. Early recognition, discontinuation of methotrexate, and timely initiation of leucovorin rescue therapy are critical to preventing severe outcomes. Regular monitoring of patients, along with close attention to possible drug interactions, is necessary to reduce the risk of toxicity. This case adds to the growing body of literature on the importance of vigilant monitoring and prompt intervention in cases of methotrexate toxicity.

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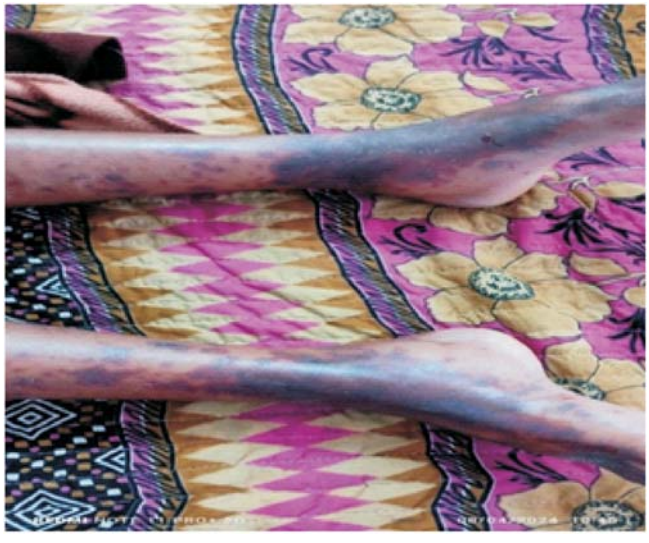
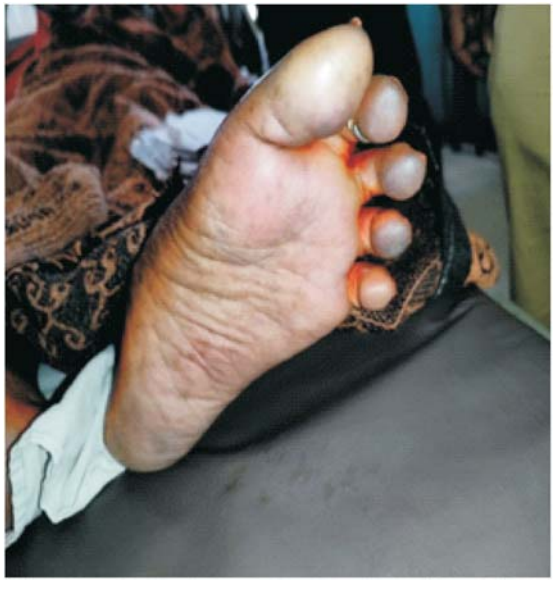
Pictorial CME

CALCIFIC UREMIC ARTERIOLOPATHY : AN UNDER RECOGNIZED ENTITY

Dr. Saswat Kumar Bahinipati[1], Dr. Asish Kumar Mohapatra[2], Dr. Binod Manthan[3]





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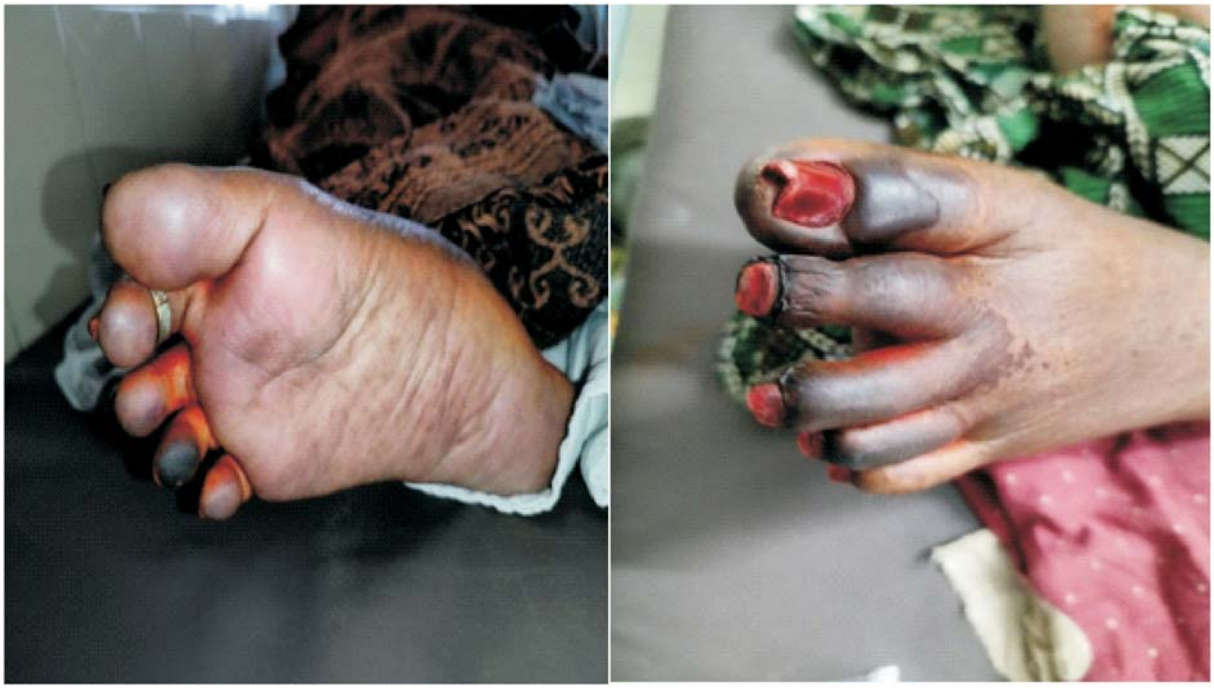

(Erythematous, violaceous skin lesions which have progressed to blackish regions of eschar formation and skin necrosis, blistering was also present in our case)

A 58 year old female who is a known case of Type 2 diabetes mellitus and ESRD on maintainance hemodialysis presented with nausea,vomiting,weakness and oliguria for last 3 days. On admission patient's urea was 106 mg/dl,creatinine was 6.2 mg/dl. In view of AKI on CKD hemodialysis (HD) was continued for 1 week every alternate day along with evaluation for inciting factor for AKI. After 1 wk of dialysis patient developed deep dull aching pain in both lower limbs especially over the distal legs and digits of the foot. Pain was followed by periods of dysasthesia and violaceous discoloration of anterior aspect of distal legs and toes. After 3 days these lesions have progressed to darkened regions of eschar formation and skin necrosis. Along with HD, supportive management was done for the skin lesions including surgical wound management, discontinuation of calcium containing phosphate binders etc.Vitamin K and zolendronic acid was given to the patient but till now these drugs are approved for off-label use. Unfortunately the patient expired because of septic complications involving the wound despite best treatment.

Calciphylaxis also known as calcific uremic arteriolopathy(CUA), is a rare life threatening vasculopathy that results from deposition of calcium in the arteriolar microvasculature of the deep dermis and subcutaneous adipose tissue. It is mostly seen in distal part of lower limbs but body parts rich in adipose tissue like abdomen and thighs are prone sites. Risk factors for CUA development include female sex, Diabetes mellitus, ESRD patients on Hemodialysis, obesity, hypoalbuminemia etc. Our patient had multiple risk factors for CUA development.Diagnosis is mainly clinical after exclusion of conditions like warfarin induced skin necrosis, cholesterol embolism syndrome, secondary vasculitis etc. In some cases Punch biopsy of skin may be required.Management options primarily focus on vigilant wound care and debridement if necrosis present to prevent secondary wound infections.Sodium thiosulfate, which is a calcium chelator reduces intra and extravascular calcification can be used for 2-3 weeks to heal those wounds, the only drug with therapeutic success in some trials. Other drugs like Vitamin K, bisphosphonates don't have any robust evidence for treatment of calciphylaxis. Prognosis of this syndrome is generally poor, if not detected and treated early.

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