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Case Report

ASSOCIATION OF NON-SECRETORY MULTIPLE MYELOMA AND HYPOTHYROIDISM: A RARE CASE REPORT

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ABSTRACT

One uncommon subtype of MM is non-secretory multiple myeloma (NSMM), and its main characteristic is the lack of observable monoclonal proteins. The coexistence of hypothyroidism and MM is very rare, and little is known about their interaction. ***Presentation of the case:*** *A known case of hypothyroidism, presented with fever, shortness of breath, and fatigue. Lytic lesions on skull X-ray, lack of proteins on protein electrophoresis, and bone marrow biopsy confirmed the diagnosis. The patient was treated with cyclophosphamide and dexamethasone.* ***Discussion:*** *This case demonstrates how challenging it can be to identify NSMM, especially when typical MM symptoms are absent. Since the concurrence of MM and hypothyroidism is very uncommon, more research is required.* ***Conclusion:*** *This study highlights the need for a multidisciplinary approach for the diagnosis and treatment of rare MM variants due to their atypical presentations. Further study is required to elucidate the underlying mechanisms and therapeutic implications of this association.*

Keywords: Hypothyroidism, Atypical Symptoms, Bone Marrow Biopsy, Non-Secretory Multiple Myeloma (NSMM)

INTRODUCTION

Clonal multiple myeloma (MM) is a type of plasma cell cancer. It makes up 10% of all haematological malignancies and is the second most common, with an incidence ranging from 0.54 to 5.3 per 100,000 people. For the past 25 years, there has been a noticeable increase in its incidence (1, 2). There are two types of multiple myeloma: secretory and non-secretory, which are based on immunoglobulin secretion. The latter group, which made up 1–2% of all cases, includes those in which the multiple myeloma criteria are met but the serum paraprotein levels stay within the normal range (3).
Numerous organs and systems of the body, including the blood, bones, and kidneys, are involved in the presentation of multiple myeloma, leading to a wide range of systemic manifestations. The diagnosis is made using the standards listed in **Table 1.**

Table 1: Diagnostic criteria for multiple myeloma (4).

Diagnostic criteria for multiple myeloma
A biopsy-verified extramedullary plasmacytoma or at least 10% of clonal bone marrow plasma cells in addition to one or more myeloma-defining events (MDE):
1. Proof of end-organ damage according to the CRAB criteria
2. Evidence of one or more high-risk biomarkers: • Bone marrow infiltration of at least 60% plasma cells; • Involved/uninvolved serum free light chain (FLC) ratio of at least 100 (assuming involved FLC is at least 100 mg/L). • Magnetic resonance imaging of multiple abnormal focal bony lesions (>5mm in size)
CRAB=hypercalcemia, renal failure, anaemia, lytic bone lesions

Patients classified as having smouldering myeloma are those with clonal bone marrow plasma cells in the range of 10–60% or serum paraprotein of >30g/L, provided they do not meet the criteria of myeloma-defining events. While secretory myelomas make up the majority, 1-2% are non-secretory, meaning they do not have serum or urine monoclonal proteins for immunofixation and electrophoresis (5, 6).
The traditional criteria for non-secretory myeloma include clonal bone marrow plasma cells ≥10% or biopsy-proven plasmacytoma; additionally, it includes evidence of end-organ damage, such as hypercalcemia, renal insufficiency, anaemia, or bone lesions, that can be linked to the underlying plasma cell proliferative disorder; and finally, the absence of serum and urinary monoclonal protein on electrophoresis and immunofixation (7).
Hypoparathyroidism is a rare endocrine disorder. Hypocalcaemia, hyperphosphatemia, and low or abnormally normal parathyroid hormone (PTH) levels are the hallmarks of hypoparathyroidism. The three main causes of hypoparathyroidism are peripheral resistance to parathyroid hormone, parathyroid tissue destruction, and the inability to synthesise or secrete parathyroid hormone (8).
Another case report on hypoparathyroidism in a multiple myeloma patient was published in 1989. This case was distinct, though, because the patient's alpha-interferon (alpha-INF) therapy was involved (9). This is in stark contrast to our case report, "Association of Non-Secretory Multiple Myeloma and Hypothyroidism: A Rare Case Presentation," which does not mention any such correlation between the two conditions and alpha-INF therapy.
Sometimes other abnormalities, such as those seen in POEMS (polyneuropathy, organomegaly, endocrinopathy, multiple myeloma, and skin changes) syndrome, present concurrently with multiple myeloma. Thyroid hormone abnormalities are common endocrinopathies in these syndromes (10); however, isolated hypothyroidism with multiple myeloma without other characteristic features of this syndrome is uncommon and necessitates careful screening and a multidisciplinary approach in similar clinical scenarios.
Published research hypothesized that inducing hypothyroidism inhibits cell proliferation and suggested a protective effect of subclinical hypothyroidism in multiple myeloma (MM) as a useful and unique adjunct for MM therapy (11). This makes the current study

we are writing more interesting and rare, as the patient in this study has both hypothyroidism and MM simultaneously.

PRESENTATION OF THE CASE

A 45-year-old man who had previously been treated for hypothyroidism with levothyroxine sought medical attention after experiencing chronic fatigue and dyspnoea that lasted for two months. Over time, his symptoms grew worse, especially with exertion such as by climbing stairs or walking short distances—but they got better with rest; however, there was no associated orthopnoea and paroxysmal nocturnal dyspnoea. He also had chills and rigors for two days along with a fever, which went away when he took paracetamol. Furthermore, there was an associated productive cough with yellow colour sputum having blood in it.

Following investigation, the patient's haemoglobin level was 7.1 g/dl(low), haematocrit of 23% and mean corpuscular volume (MCV) of 60.7 fl on full blood count, indicative of anaemia. The white blood cell count was mildly low with a value of 3.7 × $\times 10^3$ /ul and absolute neutrophilic count of 333(low) (**Table 2**). Given the above, the patient was managed as a case of lower respiratory tract infection with associated neutropenia in the internal medicine ward that included intravenous piperacillin + tazobactam, intravenous omeprazole for gastric protection, and oral paracetamol for fever management. As the patient had persistent symptoms of undertreated hypothyroidism supported by laboratory investigations, his dose was increased from 50mcg three tablets daily to four tablets of levothyroxine. The patient was closely monitored in the hospital according to local precautionary measures for neutropenia.

While in the hospital, the patient was extensively investigated to find out the cause of the underlying low ANC and hemoglobin levels. However, there was no evident history of causes such as dietary deficits or blood loss, but still, there were symptoms of anemia. Mild epigastric pain prompted a stool occult blood test, which returned negative. A peripheral smear study showed hypochromia, microcytosis, and a further reduction in hemoglobin, all of which pointed to abnormal red blood cell morphology 1.5% was The reticulocyte count. Suspicions were heightened by elevated inflammatory markers, such as an elevated C-reactive protein (CRP) level of 273.3 mg/dl and an elevated erythrocyte sedimentation rate (ESR) of 140 mm/1st hour.

Lytic lesions were seen on X-ray skull imaging, which suggested a possible bone pathology (**Figure 1**). Multiple myeloma remained a possibility even with normal serum protein electrophoresis (SPEP) findings and negative urine for Bence Jones proteins. A bone marrow biopsy was done, either to rule out or confirm the diagnosis. The results showed that 45% of the bone marrow population was made up of hyperplastic plasma cells and plasma blasts. Furthermore, sheets of lymphoplasmacytoid cells and mature lymphocytes were seen; the M: E (myeloid to erythroid) ratio of 3:1 (**Figure 2**). Hence, a diagnosis of multiple myeloma was established.

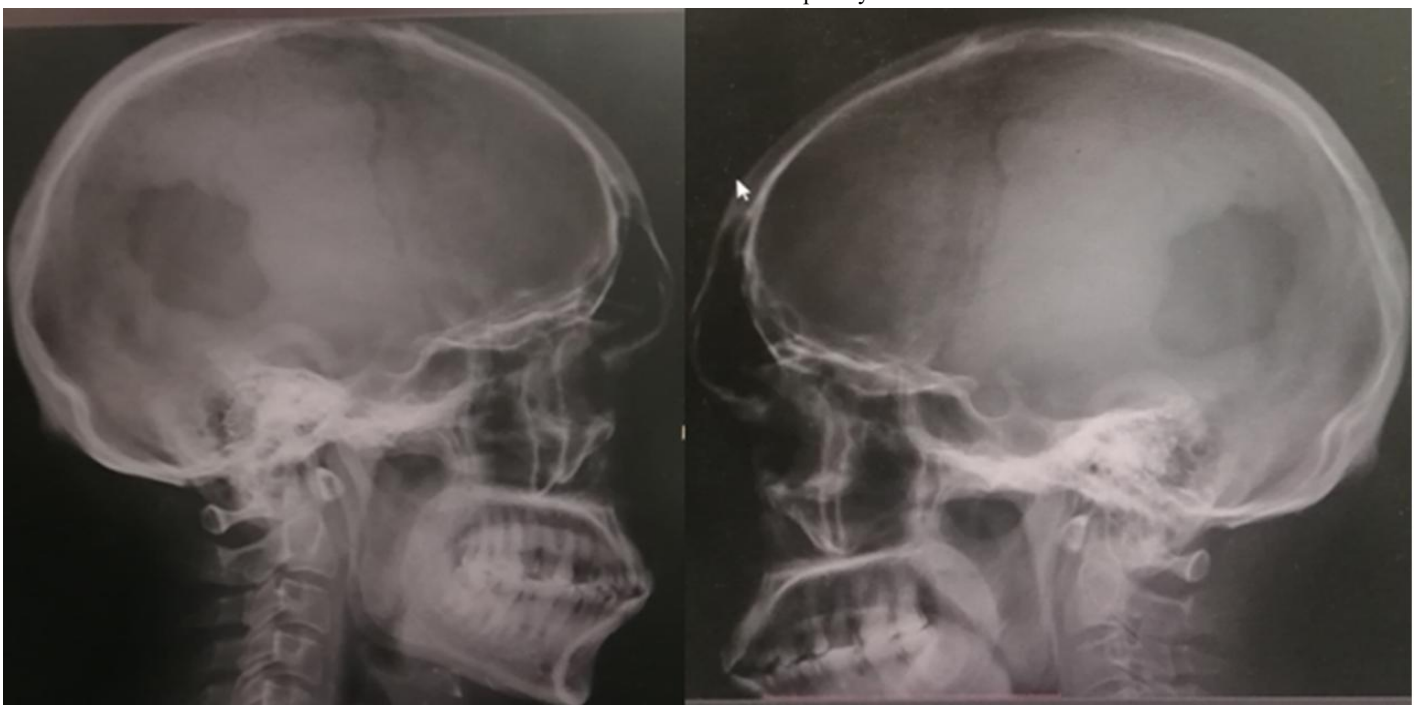

Figure 1. Skull X-ray showing Lytic lesions

For a thorough assessment, immunohistochemistry and immunofixation tests were advised; however, financial constraints made it impossible to carry them out. Following stabilization, the patient was referred to an oncologist for the management of multiple myeloma. The patient was prescribed cyclophosphamide and dexamethasone according to the patient's disease status and affordability. On follow-up, he had improved, and no side effects of the drugs were noted.

Table 2: Investigations

S. No	Test(s)	Reference range(s) and Unit(s)	Result(s)
1.	TLC	4-11×10^3 /uL	4.2
2.	Neutrophils	40-75 %	09
3.	Lymphocytes	20-45 %	86
4.	Peripheral Smear	N/A	Atypical cells, microcytosis, anisocytosis
5.	Platelets	150-450×10^3 /uL	491
6.	Sodium	135-150 mmol/L	135

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7.	Potassium	3.5-5.5 mmol/L	4.3
8.	Chloride	96-112 mmol/L	101
9.	Blood Urea	10-50 mg/dL	37.8
10.	Creatinine	0.3-0.9 mg/dL	1.11
11.	Total Bilirubin	0.1-1.0 mg/dL	1.7
12.	ALT	10-50 U/L	115.8
13.	ALP	40-129 U/L	537
14.	TSH	µIU/mL	31.41
15.	Total T3	nmol/L	0.582
16.	Free T4	pmol/L	8.03
17.	Serum Albumin	3.5-5.0 g/dL	1.99
18.	Serum Ferritin	ng/ml	63.6
19.	Serum Calcium	8.0-10.0 mg/dL	7.2
20.	Serum Vitamin B12	pg/ml	2000
21.	RBS	70-140 mg/dL	103.3
22.	Anti-HCV/Anti-HIV/HbsAg		Negative
23.	Urine R/E		Normal
24.	Stool for Occult blood		Positive
25.	H.Pylori antigen in stool		Negative
26.	LDH		265

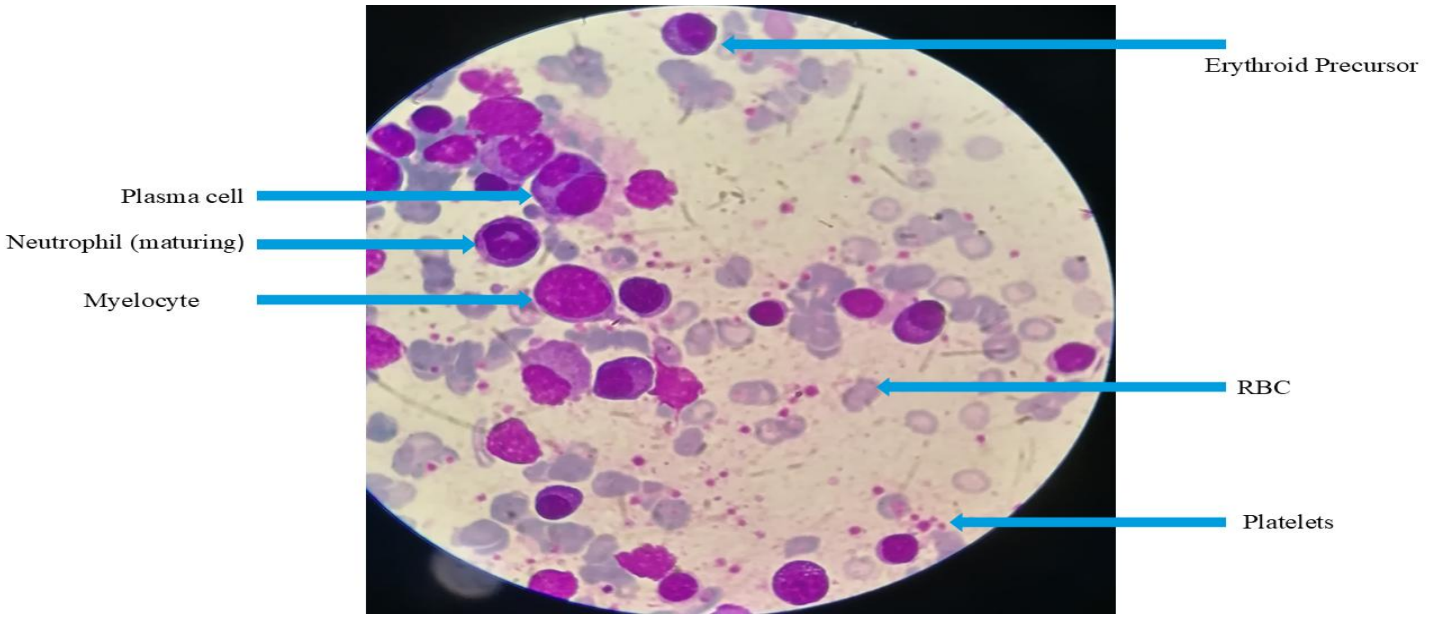

Figure 2. Bone Marrow Biopsy showing plasma cells.

CLINICAL DISCUSSION

A clonal plasma cell cancer known as multiple myeloma (MM) is typified by the infiltration of malignant plasma cells into the bone marrow, which results in a variety of systemic manifestations. (12). The rare variant known as non-secretory multiple myeloma (NSMM), which accounts for only 1-2% of cases, is difficult to diagnose because serum or urine does not contain monoclonal proteins, which are commonly used to diagnose secretory MM (3). An additional factor contributing to the unusualness of this case is the correlation our case report finds between NSMM and hypothyroidism, a rare endocrine condition.

The co-occurrence of multiple myeloma (MM) and hypothyroidism in our case creates a special and uncommon clinical situation. Low thyroid hormone levels, or hypothyroidism, are an uncommon finding in patients with multiple myeloma (MM), particularly when other hallmarks of syndromes such as POEMS (polyneuropathy, organomegaly, endocrinopathy, multiple myeloma, and skin changes) syndrome are absent (10).

Little is known about the connection between hypothyroidism and MM. In multiple myeloma, T3 and T4 promote cell proliferation and viability, and enhance cell migration and invasion (13-15). However, some research has indicated that subclinical hypothyroidism may be protective during MM treatment, perhaps as a result of its ability to inhibit cell division. A study that found a link between induced hypothyroidism and decreased cell proliferation lends credence to this theory by suggesting that hypothyroidism may be used to treat multiple myeloma (11).

Our case report adds to the scant literature on the relationship between hypothyroidism and MM. Unlike a previous case involving alpha-interferon (alpha-INF) therapy, our case makes no mention of any such correlation (9). This emphasises the necessity of further investigation to elucidate the fundamental mechanisms connecting these two conditions.

Given the rarity of this association, our case emphasises the importance of a multidisciplinary approach and careful screening for thyroid abnormalities in patients with multiple myeloma. Further

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research is required to examine the potential therapeutic implications of hypothyroidism in the management of multiple myeloma.

For two months, the patient suffered from persistent exhaustion, dyspnoea, and fatigue. Over time, his symptoms got worse, especially after doing physical activities like going for short walks or climbing stairs, but they got better after he rested. There was no orthopnoea or paroxysmal nocturnal dyspnoea. This 45-year-old male patient, however, did not exhibit any bony symptoms, such as bone pain, in contrast to the majority of MM presentations. An increased number of patients with multiple myeloma seek medical attention due to pain (16) than other haematological cancers (17, 18). Consequently, this case is made even more unique by the absence of bone pain.

In this instance, there were no classic MM symptoms present, such as renal insufficiency. The patient had anaemia, which is common in people with MM. However, there were no other symptoms, such as hypercalcemia, that are typically associated with MM (4).

There were several significant differences between our rare case report and monoclonal gammopathy of undetermined significance (MGUS). While MGUS is defined as having serum monoclonal protein (M-protein) levels of less than 3 g/dL, plasma cell counts in the bone marrow of less than 10%, minimal or no M-protein (Bence Jones protein) in the urine, no lytic lesions, anaemia, hypercalcemia, and renal insufficiency, and, most importantly, stable M-protein levels without the development of other abnormalities (19)Our case report showed unique characteristics. Specifically, our case report did not present with Bence Jones proteins, hypercalcemia, renal insufficiency, or bone pain. Nevertheless, our case did show anaemia and lytic lesions in the bones, which are not typical of MGUS (19). We, therefore, did not diagnose MGUS in our case.

Monoclonal proteins, indicative of non-secretory MM, were not detected by serum protein electrophoresis (SPEP) or urine protein electrophoresis (UPEP) (7). Since both SPEP and UPEP were normal in our instance, NSMM presents a diagnostic challenge.

X-rays and other imaging studies are crucial for assessing bone involvement in multiple myeloma (MM). In our instance, lytic lesions—a characteristic of MM—were seen on the X-ray (**Figure 1**). A bone marrow biopsy was done, either to rule out or confirm the diagnosis. The results showed that 45% of the bone marrow population was made up of hyperplastic plasma cells and plasma blasts (**Figure 2**). The bone marrow biopsy revealed that ≥10% of the cells were clonal plasma cells, which satisfied the MM diagnostic requirements (7). Financial limitations prevented immunotyping (IT), which might have revealed more information about the disease phenotype.

This case is extremely rare because there are no typical signs, symptoms, or diagnostic findings associated with MM. Diagnosing NSMM can be challenging and often requires combining laboratory, imaging, and clinical data. The patient in our case did not show other common manifestations that are commonly seen in patients with multiple myeloma (MM), such as hypercalcemia, renal insufficiency, and bone pain. Bence Jones proteins are rarely absent from urine protein electrophoresis (UPEP) samples from MM patients. Despite the lack of detectable monoclonal proteins, the patient met the diagnostic criteria for multiple myeloma (MM) because of clonal plasma cells in the bone marrow and other myeloma-defining events (MDE). This unique presentation highlights the importance of considering NSMM in the differential diagnosis of patients presenting with suggestive symptoms, even in the absence of typical laboratory results.

CONCLUSION

This singular case report sheds light on the rare coexistence of hypothyroidism and non-secretory multiple myeloma (NSMM), emphasising the challenges associated with diagnosis and the importance of considering atypical MM presentations. A multidisciplinary approach is necessary for the diagnosis and treatment of NSMM because the condition lacks detectable monoclonal proteins. This case highlights the need for more research to elucidate the underlying mechanisms and therapeutic implications of the association between NSMM and hypothyroidism. A more thorough understanding of this relationship may lead to innovative treatment strategies for multiple myopathies. Therefore, to improve patient outcomes and broaden our understanding, more research into uncommon variants of MM is required.

DECLARATIONS

Data Availability Statement

All data generated or analysed during the study are included in the manuscript.

Ethics approval and consent to participate

Approved by the department Concerned.

Consent for publication

Approved

Funding

Not applicable

CONFLICT OF INTEREST

The authors declared an absence of conflict of interest.

AUTHOR CONTRIBUTION

Farhan Shahzad
Writing manuscript, Conceptualization, Final proofreading.
Najib Ullah
Supervision, Conceptualization, Review and editing, Final proofreading.
Muhammad Yousaf
Writing the paper, Conceptualization, and Final proof reading.
Muhammad Aitizaz
Review and editing, Conceptualization, Final proofreading.
Mohammad Zamrood Khan
5Review and editing, Conceptualization, Final proofreading.
Farid Ullah
Data Curation, Conceptualization, and Final proof reading.

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