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**Case Report**

# Coexistence of Prefibrotic Myelofibrosis with Monoclonal Gammopathy of Undetermined Significance: A Case Report

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## Keywords

Myeloproliferative neoplasm · Prefibrotic phase of primary myelofibrosis · Monoclonal gammopathy of undetermined significance · Coexistence · Second malignancies

## Abstract

The coexistence of dual hematological neoplasms is an unusual and challenging presentation due to the different combination of etiopathology. The presentation of synchronous dual hematological malignancies can be one of the 3 types: myeloid + lymphoid or dual lymphoid or dual myeloid. Here, we are reporting a case of a 53-year-old male with simultaneous presence of JAK*2 V617F*-positive myeloproliferative neoplasm with features favoring prefibrotic phase of primary myelofibrosis (pre-PMF) in combination with monoclonal gammopathy of undetermined significance (MGUS). In such cases of simultaneous existence of dual hematological neoplasm management, it is recommended to treat the more aggressive one. Currently, our management plan is focusing on treating the pre-PMF and observation of MGUS with regular monitoring for transformation to MM.



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## Introduction

The hematopoietic pluripotent stem cell has both capability of self-renewal and stepwise differentiation to either lymphoid or myeloid lineage [1]. The WHO 2016 classification of myeloproliferative neoplasms (MPNs) has 7 subcategories that include chronic myeloid leukemia, chronic neutrophilic leukemia, essential thrombocythemia (ET), polycythemia vera, primary myelofibrosis (PMF), chronic eosinophilic leukemia-not otherwise specified, and MPN unclassifiable [2].

Philadelphia-negative MPNs are a heterogeneous group of hematological malignancy showing expansion and clonal proliferation of one or more hematopoietic lines [3]. Prefibrotic myelofibrosis (pre-PMF) is a special structure among chronic MPNs according to the revised 2016 WHO classification. It has heterogeneous clinical presentation that varies from isolated thrombocytosis, similar to ET, up to symptoms of high-risk PMF. Retrospective studies showed that survival of patients with pre-PMF is worse than that of ET and better than overt PMF [4].

Monoclonal gammopathy of undetermined significance (MGUS) is a premalignant asymptomatic disorder characterized by the presence of a monoclonal protein (M-protein) in the absence of end-organ damage that can be attributable to plasma cell proliferation. It is defined by the presence of a serum monoclonal immunoglobulin level under 30 g/dL and <10% clonal plasma cells in the bone marrow, with absence of amyloidosis or multiple myeloma criteria (or Waldenstrom macroglobulinemia in case of IgM MGUS) [5]. Up to our knowledge, there is no publication reporting the coexistence of prefibrotic myelofibrosis with MGUS in the literature.

## Case Presentation

We report a case of a 53-year-old Qatari male with a medical background of hypertension, dyslipidemia, diabetes mellitus type 2, and hypothyroidism under hormonal therapy (levothyroxine), referred to hematology due to unexplained persistent increase in platelet count for almost 1 year starting from October 2018. He had frequent presentations to emergency with chest pain and fatigue. He denies constitutive symptoms, itching, sweating, loss of weight, and nocturnal fever. Clinical examination did not reveal any significant finding and was unremarkable with no palpable liver, spleen, or lymph nodes, and his laboratory test is shown in Table 1.

Serum protein electrophoresis showed normal albumin. There was a monoclonal band typed and proved to be IgG kappa. The size of the band was about 3.1 g/L. There was no electrophoretic evidence of hypogammaglobulinemia. Urine 24-h protein electrophoresis did not show any band suggestive of free light chains and was considered to be negative for Bence Jones protein.

Molecular testing was positive for *JAK2 V617F* missense mutation and negative for insertion/deletion mutation within exon 9 of the *CALR* gene and *BCR-ABL1* gene fusion by single-step RT-PCR. Chromosomal analysis by the banding technique on 30 cells from a bone marrow sample revealed a normal male karyotype 46, XY. PET CT showed no sign of FDG-avid malignancy.

Peripheral blood showed moderate thrombocytosis, otherwise unremarkable. Bone marrow aspirate was cellular with trilineage hematopoiesis and increased megakaryocytes with anisocytosis and pleomorphism, some atypia, and including many large forms with abundant cytoplasm and hyperlobulated nuclei. Plasma cells were increased (7%). Bone marrow biopsy showed variable cellularity with an average of 55% which is mildly increased for age and showing trilineage hematopoiesis, increased megakaryocytes with clustering, many large forms, and some smaller ones with mild atypia (Fig. 1A, B). CD138 immunostain highlighted the increased plasma cells (Fig. 2) comprising approximately 5–10% of

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**Table 1.** Laboratory investigations

| Test name | Result | Normal values |
|---|---|---|
| ECOG | 1–2 | |
| Hematology | | |
| White blood cell, $\times 10^3/\mu L$ | 6.98 | 4–10 |
| Hemoglobin, g/dL | 15 | 13–17 |
| Platelets, $\times 10^3/\mu L$ | 852 | 150–400 |
| ANC, $\times 10^3/\mu L$ | 3.0 | 2–7 |
| Lymphocytes, $\times 10^3/\mu L$ | 3.0 | 1–3 |
| Monocytes, $\times 10^3/\mu L$ | 0.4 | 0.2–1 |
| Eosinophils, $\times 10^3/\mu L$ | 0.2 | 0–0.5 |
| Chemistry | | |
| Creatinine, μmol/L | 72 | 70–115 |
| Total protein, g/L | 75 | 60–80 |
| Total bilirubin, μmol/L | 9.7 | 0–21 |
| ALT, U/L | 20 | 0–40 |
| AST, U/L | 23 | 0–37 |
| Corrected calcium, mmol/L | 2.4 | 2.1–2.6 |
| LDH, U/L | 301 | 135–225 |
| Albumin, g/L | 47.4 | 35–50 |
| M band in serum, g/L | 3.1 | |
| 24-h urine protein, g/24 h | 0.14 | 0.03–0.15 |
| Bence Jones protein, g/L | Negative | |
| Serum light chain kappa, mg/L | 40.3 | 3.3–19.4 |
| Serum light chain lambda, mg/L | 20.3 | 5.7–26.3 |
| Kappa/lambda | 1.99 | Ratio |

the cellularity with obvious kappa predominance (Fig. 3A, B). Molecular analysis was positive for the *JAK2 V617F* missense mutation and negative for a *BCR-ABL1* gene fusion.

Overall findings were consistent with a MPN with features favoring prefibrotic phase of primary myelofibrosis (pre-PMF). The increased plasma cells with kappa predominance favored concomitant marrow involvement by a plasma cell neoplasm. After completion of workup, the patient was diagnosed as a case of MPN with features favoring prefibrotic phase of primary myelofibrosis (pre-PMF) with increased plasma cells appearing kappa restricted fitting the diagnostic criteria of MGUS.

## Discussion

It has been observed that the number of patients who were diagnosed unexpectedly with a synchronous dual hematological malignancy is increasing, as the concurrent secondary hematological malignancies can be masked by the primary malignancy. There are only few reports of dual hematological malignancies in the literature, and usually the management of these patients is challenging. The impact of comorbidity on disease progression and outcomes remains unknown.

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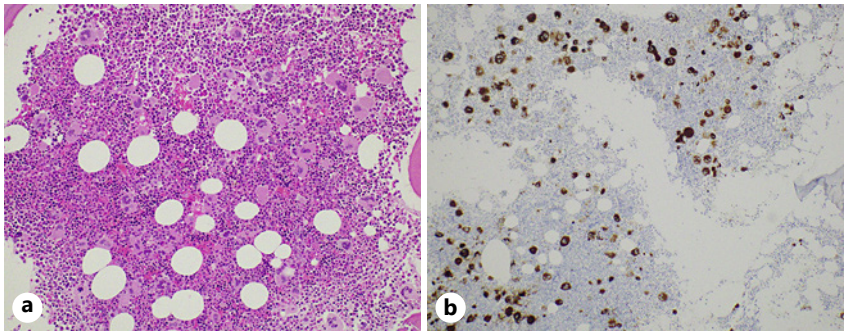


**Fig. 1. a** Bone marrow biopsy showing increased megakaryocytes with anisocytosis and atypia (H&E. ×20). **b** CD61 immunostain further highlighting the increased megakaryocytes.

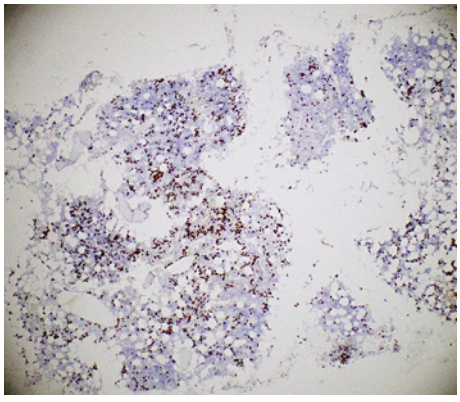

**Fig. 2.** CD138 immunostain showing the increased plasma cells comprising approximately 5–10% of the bone marrow cellularity.

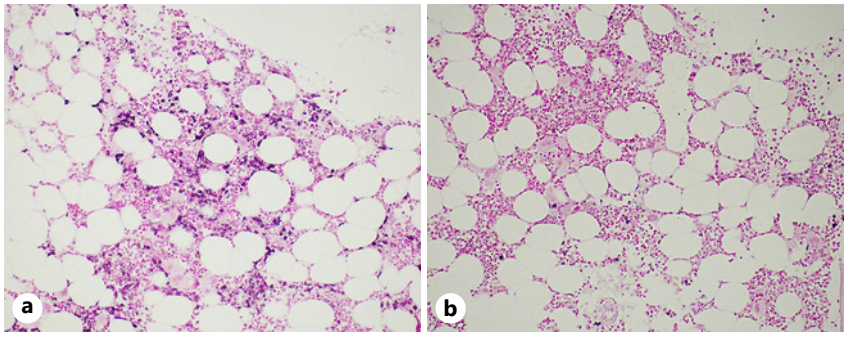


**Fig. 3. a** Kappa light chain mRNA in situ hybridization on bone marrow core biopsy showing obvious kappa predominance. **b** Lambda light chain mRNA in situ hybridization on bone marrow core biopsy showing rare positivity.

The coexistence of MPN with MGUS is reported in few cases, but the presence of prefibrotic phase of primary myelofibrosis (pre-PMF) with MGUS is not reported previously. A retrospective chart review of 3,036 patients who had hematological malignancy identified 46 patients having coexistence of dual hematological neoplasms, that is, a prevalence of 1.51% among patients with any hematological malignancy [6]. Three types of coexistence of dual hematological neoplasms were identified; among these 46 patients, 23/46 had myeloid +

lymphoid with 10 of them having MPN + MGUS, and 20/46 had lymphoid + lymphoid, and 3/46 had myeloid + myeloid.

Our patient who presented with persistent erythrocytosis and JAK2 positive expected to be ET. Bone marrow aspiration and biopsy showed features of pre-PMF. The differentiation between pre-PMF and ET is by characteristic morphological BM features of both diseases and also by the different clinical behavior. ET is a more benign entity in terms of survival, progression to myelofibrosis, and transformation to blastic phase. On the other hand, the incidence of major thrombosis in ET is comparable to pre-PMF and lower than polycythemia vera [2]. Coexistence of dual hematological neoplasms suggests increased susceptibility or impaired immunity. The majority of coexistent dual hematological neoplasms can be managed expectantly, but if both malignancies need treatment, then therapy should target the more aggressive one. Our group is studying the unmet clinical needs in Myeloproliferative neoplasms and CML [7] like cost effective analysis for second generations TKIs when used as upfront [8], the association of tuberclosis with CML [9], the reactivation of hepatitis B with CML [10], ophthalmic manifestations as initial presentation in patients with CML [11], Effects of intermittent fasting on CML [12], autoimmune hemolytic anemia and its association with different therapies in CML [13], priapism [14, 15] and male fertility [16], as well as obesity [17] and obesity related surgeries in patients with CML [18].

## Conclusion

Synchronous dual hematological malignancy is described in the literature; however, its effect on prognosis and response to different modalities of treatment need further studies. This mandates adequate reporting of all cases for better characterization and optimization of patient outcome.

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## Statement of Ethics

Written informed consent was obtained from our patient to allow the publication of information including images.

## Conflict of Interest Statement

None of the authors declared any conflicts of interest.

## Author Contributions

Omar M. Ismail contributed to writing the manuscript and literature review. Aliaa Amer and Feryal A. Ibrahim contributed to preparation of histopathology slides and final approval. Mohamed A. Yassin contributed to clinical follow-up, final editing, and final approval. Mohammad Abu-Tineh contributed to literature review and final approval.

## Data Availability Statement

Data available from authors upon request.

## References

1 Seita J, Weissman IL. Hematopoietic stem cell: self-renewal versus differentiation. Wiley Interdiscip Rev Syst Biol Med. 2010 Nov–Dec;2(6):640–53.
2 Barbui T, Thiele J, Gisslinger H, Kvasnicka HM, Vannucchi AM, Guglielmelli P, et al. The 2016 WHO classification and diagnostic criteria for myeloproliferative neoplasms: document summary and in-depth discussion. Blood Cancer J. 2018 Feb 9;8(2):15–1.
3 Yassin MA, Taher A, Mathews V, Hou HA, Shamsi T, Tuğlular TF, et al. MERGE: a multinational, multicenter observational registry for myeloproliferative neoplasms in Asia, including Middle East, Turkey, and Algeria. Cancer Med. 2020 Jul;9(13):4512–26.
4 Yassin MA, Nehmeh SA, Nashwan AJ, Kohla SA, Mohamed SF, Ismail OM, et al. A study of 18F-FLT positron emission tomography/computed tomography imaging in cases of prefibrotic/early primary myelofibrosis and essential thrombocythemia. Medicine. 2020 Nov 6;99(45):e23088.
5 Kyle RA. Monoclonal gammopathy of undetermined significance: natural history in 241 cases. Am J Med. 1978 May 1;64(5):814–26.
6 Kotchetkov R, Ellison E, McLean J, Pressnail B, Nay D. Synchronous dual hematological malignancies: new or underreported entity? Hematology. 2018 Oct 21;23(9):596–9.
7 Turkina A, Wang J, Mathews V, Saydam G, Jung CW, Al Hashmi HH, et al. TARGET: a survey of real-world management of chronic myeloid leukaemia across 33 countries. Br J Haematol. 2020 Sep;190(6):869–76.
8 Adel A, Abushanab D, Hamad A, Abdulla M, Izham M, Yassin M. Assessment of dasatinib versus nilotinib as upfront therapy for chronic phase of chronic myeloid leukemia in qatar: a cost-effectiveness analysis. Cancer Control. 2021;28:10732748211001796.
9 Iqbal P, Soliman A, De Sanctis V, Yassin MA. Association of tuberculosis in patients with chronic myeloid leukemia: a treatment proposal based on literature review. Expert Rev Hematol. 2021;14:211–7.
10 Atteya A, Ahmad A, Daghstani D, Mushtaq K, Yassin MA. Evaluation of Hepatitis B reactivation among patients with chronic myeloid leukemia treated with tyrosine kinase inhibitors. Cancer Control. 2020;27(1):1073274820976594.
11 Yassin MA, Ata F, Mohamed SF, Alkhateeb A, Naeem U, Al-Qatami AI, et al. Ophthalmologic manifestations as the initial presentation of chronic myeloid leukemia: a review. Surv Ophthalmol. 2021;S0039–6257–2.
12 Yassin MA, Ghasoub RS, Aldapt MP, Abdulla MA, Chandra P, Shwaylia HM. Effects of intermittent fasting on response to tyrosine kinase inhibitors (TKIS) in patients with chronic myeloid leukemia: an outcome of european leukemianet project. Cancer Control. 2021;28:10732748211009256.
13 Hamamyh T, Yassin MA. Autoimmune hemolytic anemia in chronic myeloid leukemia. Pharmacology. 2020;105:630–8.
14 Ali E, Soliman A, De Sanctis V, Nussbaumer D, Yassin M. Priapism in patients with chronic myeloid leukemia (CML): a systematic review. Acta Biomed. 2021;92(3):e2021193.
15 Ali EA, Nashwan AJ, Yassin MA. Essential thrombocythemia with (type 2) calreticulin presented as stuttering priapism case report and review of literature. Clin Case Rep. 2021;9:399–404.
16 Yassin MA, Soliman AT, De Sanctis V. Effects of tyrosine kinase inhibitors on spermatogenesis and pituitary gonadal axis in males with chronic myeloid leukemia. J Cancer Res Ther. 2014;2:116–21.
17 Abdulla M, Chandra P, Akiki S, Sorio C, Tomasello L, Boni C. Clinicopathological variables and outcome in chronic myeloid leukemia associated with BCR-ABL1 transcript type and body weight: an outcome of european leukemia net project. Cancer Control. 2021.
18 Yassin MA, Kassem N, Ghassoub R. How I treat obesity and obesity related surgery in patients with chronic myeloid leukemia: an outcome of an ELN project. Clin Case Rep. 2021;9:1228–34.