

# Essential Thrombocythaemia with Concomitant Waldenström Macroglobulinaemia: Case Report and Literature Review

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Nina Lu<sup>1</sup>  
Chin Loon Neoh<sup>2</sup>  
Zhengying Ruan<sup>3</sup>   
Lei Zhao<sup>4</sup>  
Limei Ying<sup>1</sup>  
Xiaochang Zhang<sup>1</sup>  
Sai Chen<sup>1</sup>  
Linglong Xu<sup>1</sup> 

<sup>1</sup>Department of Hematology, Taizhou Central Hospital (Taizhou University Hospital), Taizhou, Zhejiang 318000, People's Republic of China; <sup>2</sup>Department of Hematology, Royal Marsden Hospital, London SW3 6JJ, UK; <sup>3</sup>Department of Pathology, Taizhou Central Hospital (Taizhou University Hospital), Taizhou, Zhejiang 318000, People's Republic of China; <sup>4</sup>Department of Laboratory Medicine, Taizhou Central Hospital (Taizhou University Hospital), Taizhou, Zhejiang 318000, People's Republic of China

**Abstract:** Essential thrombocythaemia (ET) and Waldenström macroglobulinaemia (WM) are two distinct disorders. Studies have reported several cases of myeloproliferative neoplasms (MPNs) with concomitant plasma cell dyscrasia. However, there were no reported cases of ET with concomitant WM to date. Here, we present a 55-year-old Chinese man with thrombocytosis and raised immunoglobulin level. Further investigations led to a diagnosis of ET and coexistent WM. Next-generation sequencing (NGS) of his bone marrow identified 3 mutated genes: JAK2 V617F, MYD88 L265P, and ATM F1036L. After being treated with pegylated interferon and low-dose aspirin, his platelet count normalized and immunoglobulin M (IgM) level reduced. To the best of our knowledge, this is the first reported case of dual pathology ET with WM.

**Keywords:** myeloproliferative neoplasm, Waldenström macroglobulinaemia, Janus kinase 2, myeloid differentiation factor 88

## Introduction

Essential thrombocythaemia (ET) is one of the myeloproliferative neoplasms (MPNs). Waldenström macroglobulinaemia (WM) is a lymphoplasmacytic lymphoma with an IgM monoclonal gammopathy and bone marrow involvement. These are 2 distinct haematological disorders that arise from different haematopoietic clones. There were reported cases of MPNs with concomitant plasma cell disorders like monoclonal gammopathies of undetermined significance (MGUS) and multiple myeloma (MM). However, no cases of ET with coexistent WM have been reported to date.

Written informed consent was provided by the patient to publish the case details. The ethics committee of Taizhou Central Hospital approved the publication of the case details.

## Case Report

A 55-year-old Chinese man was referred to our department with a history of asymptomatic thrombocytosis over 1 year's duration. Apart from pleural tuberculosis 2 years ago treated with systemic anti-tuberculous therapy, his past medical history was unremarkable. His physical examination was unremarkable. A full blood count revealed a white blood cell count of  $9.2 \times 10^9/L$  with lymphocytes count of  $3.0 \times 10^9/L$ , haemoglobin 132g/L and platelet count of  $629 \times 10^9/L$ . Peripheral blood film showed thrombocytosis and there

Correspondence: Linglong Xu  
Email daniongnong@163.com

was no significant dysplasia. His biochemistry profile revealed a slightly raised total globulin level of 41.9g/L (normal range: 20–40g/L), uric acid: 507 $\mu$ mol/L (normal range: 208–428  $\mu$ mol/L) and lactate dehydrogenase 242U/L (normal range: 109–245U/L). His serum immunoglobulin analysis revealed an elevated immunoglobulin M (IgM) of 21.5g/L (normal range: 0.46–3.04g/L), kappa light chain of 26.8g/L and lambda light chain lambda of 5.03g/L. Serum immunofixation confirmed the presence of monoclonal IgM. Ultrasound imaging study did not reveal lymphadenopathy, hepatomegaly or splenomegaly.

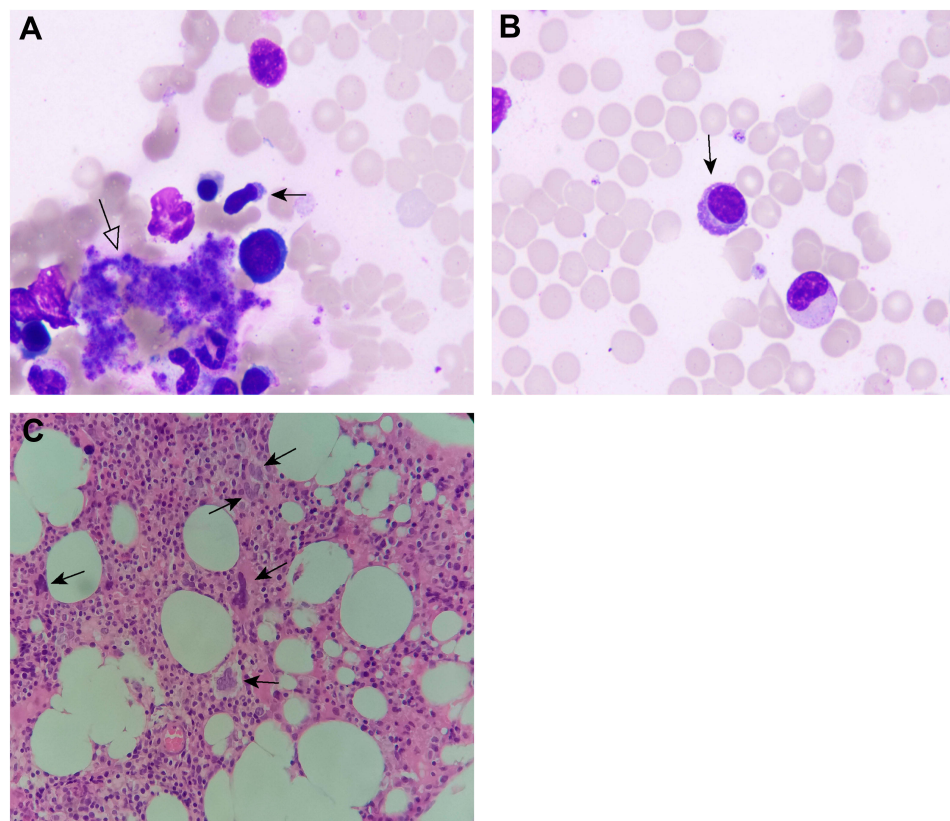
A bone marrow (BM) aspiration and trephine biopsy were performed. The BM aspirate morphology showed an excess of platelets and lymphoplasmacytoid lymphocytes (Figure 1A and B). The trephine reported cellularity of 55%, with increased numbers of lymphocytes and mature megakaryocytes with hyperlobated nuclei (Figure 1C). Flow cytometric immunophenotyping of his BM aspirate confirmed monoclonal B lymphocytes, which were positive for CD19, CD20 and cell membrane kappa light chain, but

negative for CD5, CD10 and CD23 (Figure 2). Next-generation sequencing (NGS) with a 126-mutation panel was adopted to further investigate his gene/molecular mutation status which detected JAK2 V617F, MYD88 L265P, and ATM F1036L. BCR-ABL1 mRNA was not detected by quantitative real time-PCR.

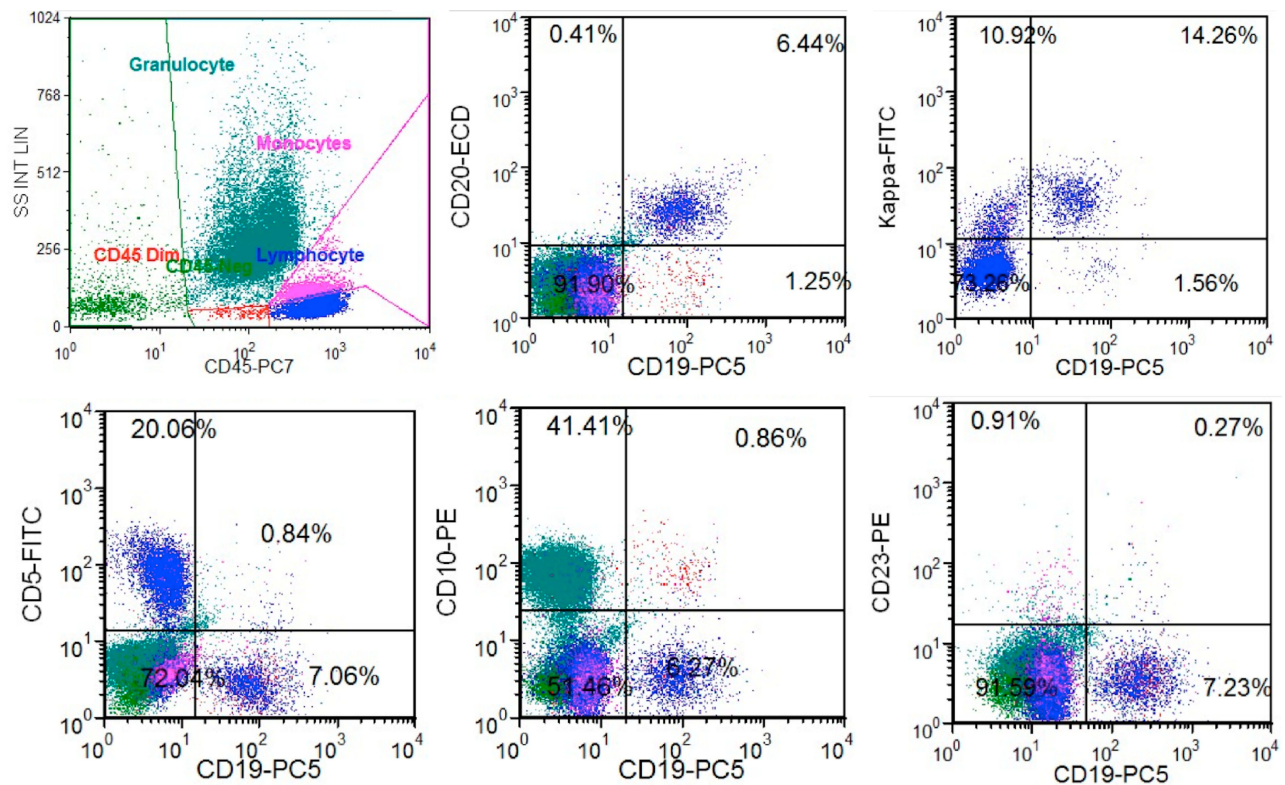
Taken together, a diagnosis of ET with concomitant WM was made. He was treated with pegylated interferon and low-dose aspirin (100mg per day). After two months of treatment, his platelet count dropped to 324 $\times$ 10<sup>9</sup>/L and IgM level to 11.80g/L.

## Discussion

ET is characterized by clonal hematopoiesis thrombocytosis and susceptibility to thrombosis. About 50% of ET patients demonstrate JAK2 V617F mutation. Although JAK2 V617F is more commonly seen in MPN, it can also be found in other myeloid malignancies, such as acute myeloid leukemia and myelodysplastic syndrome. This patient met the WHO 2016 diagnostic criteria of ET



**Figure 1** Histological examination of the bone marrow. (A) The bone marrow aspiration shows an excess of platelets (white arrow) and a lymphoplasmacytoid lymphocyte (black arrow), which has a shoe shaped cell with pale blue cytoplasm and an irregular nucleus (giemsa staining;  $\times$ 1000). (B) A lymphoplasmacytoid lymphocyte (black arrow) with pale blue cytoplasm and an eccentric nucleus (giemsa staining;  $\times$ 1000). (C) The bone marrow trephine shows increased numbers of lymphocytes and an excess of mature megakaryocytes with hyperlobulated nuclei (black arrow; hematoxylin and eosin staining;  $\times$ 400).



**Figure 2** Flow cytometry immunophenotyping result of the bone marrow. The flow cytometry confirmed the presence of monoclonal B lymphocytes, which were positive for CD19, CD20 and cell membrane light chain kappa, but negative for CD5, CD10 and CD23. Blue dots denote lymphocytes.

with thrombocytosis, typical bone marrow finding, exclusion of BCR-ABL1 and presence of JAK2 V617F.<sup>1</sup>

WM is an indolent B cell neoplasm with an MYD88 L265P mutation.<sup>2</sup> Although this mutation is not strictly required for the diagnosis of WM, it is found to be highly characteristic and present in about 90–95% of cases. When taken into consideration the BM aspirate morphology, immunophenotype, presence of IgM gammopathy and MYD88 mutation, a diagnosis of WM can be made in this patient. It remains important to note that MYD88 L265P can exist in a minority of other low-grade B cell neoplasms such as chronic lymphocytic leukaemia (CLL), mantle cell lymphoma (MCL), splenic margin zone lymphoma and follicular lymphoma.<sup>3–6</sup>

It is unclear if MPN directly correlates with lymphoid neoplasms. On reviewing some literature, the reported cases of MPN coexist with MGUS or MM.<sup>7</sup> Eskazan AE et al reported a patient with ET developed MM after being treated with hydroxycarbamide for 3 years.<sup>8</sup> Kuroda J et al also reported a case with concomitant ET and MM in which both the haematological neoplasms were shown to originate from separate malignant clones at hierarchically different differentiation levels.<sup>9</sup> There are other case reports and reviews reporting patients with coexisting MPN and plasma

cell disease.<sup>10</sup> Overall, most patients in these cases were over 55 years old. It seems that concomitant plasma cell diseases do not accelerate the evolution of MPN to blastic phase. And there is no definitive evidence showing that these 2 entities arise from a common-ancestor hematopoietic stem cell.<sup>7,9,10</sup> The management of these patients should be individual based. We treated the patient with pegylated interferon and aspirin. And he had his thrombocytosis and IgM level ameliorated after 2 months' treatment. However, further study is warranted to establish optimal management.

The mechanism of developing MPN with concomitant plasma cell dyscrasia remains to be elucidated. Recent studies indicate that oxidative stress plays a major role in carcinogenesis as well as in genomic instability. Chronic inflammation, oxidative stress might trigger the clonal evolution in MPN.<sup>11–13</sup> An increased level of reactive oxygen species (ROS) and inflammation markers were observed in ET patients.<sup>14,15</sup> ROS levels and total antioxidant capacity seemed to be reduced after current risk-adapted therapy.<sup>16</sup> On the other hand, there are growing data to support external microbial and antigen stimulation can trigger the development of lymphoproliferative diseases, including WM.<sup>17,18</sup> Perrot A found that a peroxidase PRDX6 was most under-



expressed in WM, which indicates oxidative stress might contribute to the pathogenesis of WM.<sup>19</sup>

ATM, which controls genome stability and cell survival, is part of cell metabolism and growth and oxidative stress.<sup>20</sup> Oxidation can activate ATM directly.<sup>21</sup> ATM-deficient mice show elevated ROS, indicating ATM can reduce oxidative stress.<sup>22</sup> In this case, the patient gained an additional ATM F1036L mutation, which might correlate to the excess of oxidative stress. Taken together, oxidative stress might play a role in the development of co-occurrence of ET and WM in the patient. And further study is warranted.

The previous study reported MPN patients can develop secondary malignancy, including squamous cell carcinoma, basal cell carcinoma, bladder cancer, rectal carcinoma, and hematological malignancy. A propensity score weighted competing risk analysis revealed a statistically significant increased risk of second malignancy (HR 10.81 [95% CI 2.54–45.92],  $p=0.001$ ) with ruxolitinib treatment.<sup>23</sup> However, such data should be interpreted with caution, because of the very low prevalence of secondary malignancy. Of note, the use of JAK1/2 inhibitor seems to be associated with a higher frequency of aggressive B-cell lymphomas. Porpaczy E et al conducted a retrospective study and found that B-cell lymphomas evolved in 4 (5.8%) out of 69 patients receiving JAK1/2 inhibitor compared to 2 (0.36%) of 557 patients with conventional treatment (hence, a 16-fold increased risk).<sup>24</sup>

## Conclusion

To the best of our knowledge, MYD88 L265P is seen in JAK2 V617F positive ET. The case we present is the first case of ET with coexistent WM. It is not clear whether these two conditions originate from the same or separate malignant clones. As such, the management of such cases should be individualized as there is insufficient evidence to guide treatment.

## Disclosure

The authors have no conflicts to declare.

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