

## Case Report

# Multiple myeloma developing during long-term clinical course of refractory immune thrombocytopenic purpura: a case report and review of literature

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**Abstract:** Immune thrombocytopenia (ITP) is an acquired, immune-mediated disease that is characterized by increased destruction of platelets by autoantibodies. Although the onset of the disease and clinical course are highly variable, the disease typically has a benign course. ITP associated with multiple myeloma (MM) has been rarely reported; it is even rarer for MM to develop during a long-term ITP (almost 20 years). Here, we first report on a case with a 20-year long clinical course of refractory ITP followed by newly diagnosed MM.

**Keywords:** Immune thrombocytopenic purpura, multiple myeloma, immunosuppression, bortezomib

### Introduction

Immune thrombocytopenia (ITP) is an acquired, immune-mediated disease that is characterized by increased destruction of platelets by autoantibodies. Although the onset of the disease and clinical course are highly variable, the disease typically has a benign course. Therefore, we first report on a case with a 20-year long clinical course of refractory ITP followed by multiple myeloma (MM).

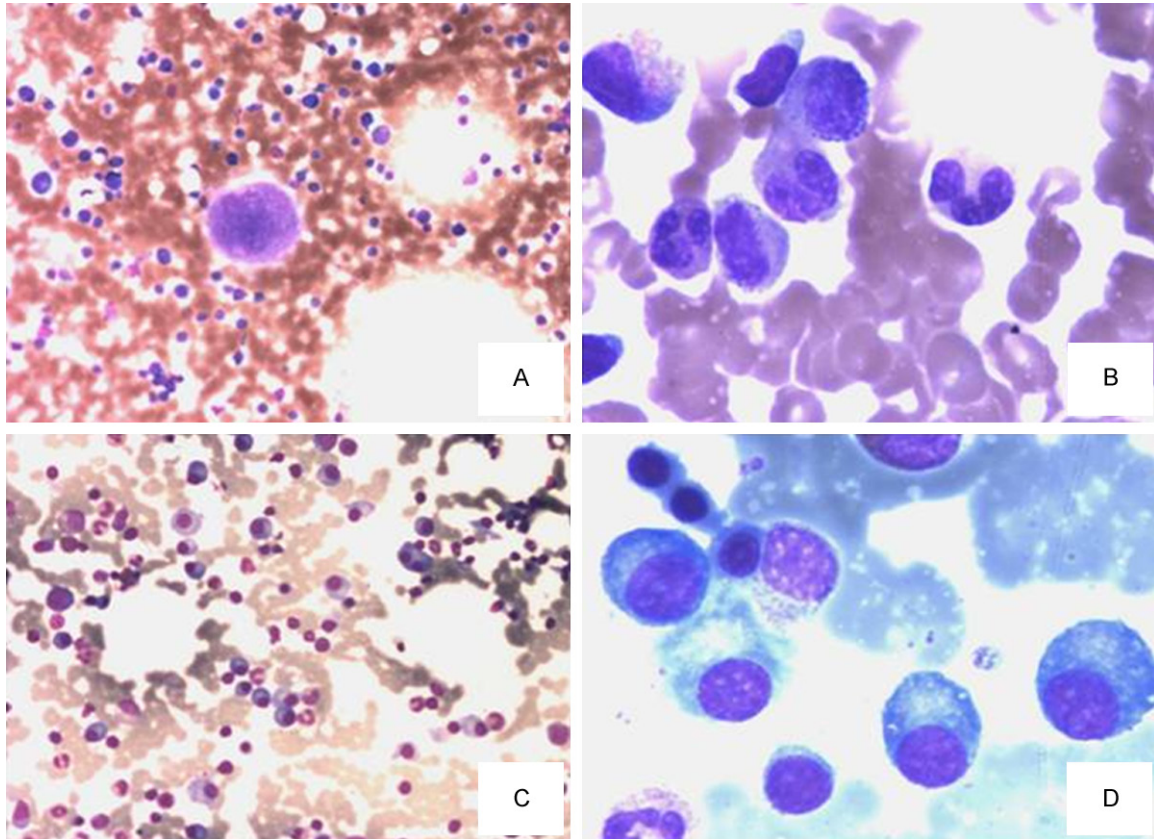
### Case presentation

A 61-year-old Chinese man was diagnosed ITP in our clinic in 1994; he had the initial symptoms of petechiae after a slight scratch or crash, bleeding gums, and minor nosebleeds. He lacked symptoms such as fever, fatigue, palpitation, bone aches, bloating or melena. The routine platelet count was  $27 \times 10^9/L$  and PAlGg is 750 ng/ $10^7$  PA. The bone marrow aspiration showed macrophage maturation obstacles with no clusters of mature plasma cells, and the patient was diagnosed with ITP. He was treated with prednisone, and the bleeding was alleviated, but there was no alteration in the platelet count. During 1995, he received a high dose of intravenous immunoglobulin (IVIG) and

methylprednisolone as well as was maintained with danazol and interferon (IFN). In response the PLT recovered shortly; soon after, it returned to a fairly low level, which could be exacerbated by cold or fatigue. As a result, he underwent splenectomy and his platelet count, after an initial increase, fell below  $30 \times 10^9/L$ . He was diagnosed with refractory ITP. During 1997, he was treated with azathiopurine and IFN, and the platelet count slightly increased. In 1999, a 4-day regimen of vincristine and dexamethasone (VD) regimen was chosen. The platelet count returned to  $60-100 \times 10^9/L$  and was decreased after one month. Until 2000, the former therapy seemed to have little effect and was taken irregularly. During 2000 to 2007, the patient was admitted to the hospital for pulmonary infection and gastrointestinal hemorrhage, respectively, and he was treated with 35 mg of prednisone and 0.5 mg of tacrolimus, which failed to improve the platelet count. Of note, he developed a lower backache, hepatalgia, and a decrease in hemoglobin (85 g/L), but bone marrow aspiration suggested there was no alteration, except for ITP, in 2005.

In August 2014, the patient was admitted to our clinic in a wheelchair for high fever and intense ostalgia with dysfunction in both the neck and

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**Figure 1.** Bone marrow (BM) aspirate of the patient. A, B: BM aspiration performed in 2005, showing plasma cell maturation obstacles, diagnosed as ITP; C, D: BM aspiration performed in 2014, showing an increasing ratio of the plasma cells; the patient was diagnosed with MM.

lower lumbar region. A reverse ratio of A/G was noted without impairment in liver function. We re-checked the bone marrow aspirate and biopsy, which show an elevated ratio (9%) of mature plasma cells, double nucleus plasma cells, and increasing megakaryocytes with maturation obstacles (**Figure 1**). The IgG level was 60.5 g/L, and immunofixation electrophoresis showed a monoclonal sedimentation of IgG kappa light chain, serum immuno-fixation of albumin of 33.9%, and  $\beta$ -2 microglobulin of 22.9 mg/d. PET/CT show an increased glucose metabolism of the whole body bone and pathologic changes of L3; the gene detection of IGH and MYC rearrangement and Bence-Jones proteinuria was negative, and cardiac ultra-sonography suggests enlargement of both atria, which was diagnosed as multiple myeloma (MM, IgG ISS II; DS IIIA). Not waiting for platelet recovery, a standard VTD (Bortezomib 1.3 mg/m<sup>2</sup> d1, 4, 8, 11; Thalidomide 100 mg/d d1-21; and Dexamethasone 40 mg/d d1-4, 8-11) was immediately used to treat MM. After 2 courses

of VTD treatment, the bone pain disappeared, and the comprehensive evaluation of MM indicated partial response. Prednisone (30 mg per day) was chosen to improve the platelet levels, but it had little effect. After the third course of VTD, IVIG was chosen for treating ITP with little effect. Of note, there was no bleeding, such as melena or petechiae. Treatment of the two diseases was still ongoing.

### Discussion

ITP associated with MM has been rarely reported [1]; it is even more rarely for MM to develop during a long-term ITP (almost 20 years). Here, we report on a long duration of refractory ITP followed by newly diagnosed MM. Although ITP and MM are both derived from B lymphocytes, we could not conclude the reason of MM for this patient.

ITP is caused by immune-mediated platelet destruction and impaired platelet production,

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causing thrombocytopenia and occasional bleeding [2]. Immunosuppressive drugs are the first choice for the treatment of ITP. The application of immunosuppressive drugs can lead to the decline of immune function of the body. In this case, the immune function is very poor for the long-term use of prednisone, tacrolimus, rituximab and other immunosuppressive drugs. Studies have shown that the occurrence of MM is related to immunosuppression [3]. In particular, the risk of MM in HIV patients is increased 4.5-fold compared with the general population [4]. So, we suspect that the occurrence of MM in the patient with long-term use of immunosuppressive agents. With respect to the proceedings of monoclonal gammopathy of undetermined significance (MGUS), smoldering MM (sMM) to MM, it is believed that the initial genetic mutations in MM take place in the germinal center (GC) during the process of somatic hypermutation and isotype switching. The mutated clone post-GC mutated B cell then homes to the bone marrow, where it completes differentiation in long-lived plasma cells (PCs) and acquires further mutations during the evolution from MGUS to sMM and then to MM [5]. In this case, the progression from sMM or MGUS is absent. It is difficult to determine whether this is from the disease or lack of early comprehensive examination. It is a pity that although the patient had bone ache early in the disease progression, PET-CT and MRI, both of which are highly sensitive for detecting MM-related bone lesions, making early detection of the MM more likely, were unavailable. Fortunately, the abnormality in the reverse ratio of A/G reminded the clinician to perform further checks.

Proteasome inhibitors, such have Bortezomib, have had a good outcome in MM [6]. The most common hematologic toxicity associated with Bortezomib is transient thrombocytopenia, which shows a cyclical pattern of platelet decrease and recovery without evidence of cumulative thrombocytopenia. The transient, predictable decrease in the platelet counts generally results in a slight requirement for platelet support. As a result, Bortezomib can usually be given to thrombocytopenic patients [7]. Refractory ITP is still difficult to treat; it has fairly low long-term non-relapse rates and accompanying toxicities [8]. In this case, the refractory ITP was not cured or improved with

standard therapy. Although the patient has not experienced serious bleeding, ITP with persistent low platelet counts has a grave prognosis [9]. In the later treatment for this patient, maintenance of the PLT count to a relatively normal level is necessary. Recombinant human thrombopoietin (TPO), in combination with Rituximab, may be tried in the treatment of ITP [10]. We will continue to perform careful observation in this case.

### Disclosure of conflict of interest

None.

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