Clin. Lab. Haem.
2000, **22**, 239–242

CASE REPORT

Multiple myeloma and immune thrombocytopenia

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Summary Immune thrombocytopenia (ITP) is frequently encountered in patients with lymphoproliferative disorders. However this is only rarely reported in patients with multiple myeloma. We describe three cases who presented initially with the clinical manifestations of ITP but were subsequently found to have multiple myeloma. Platelet count increments to standard treatment modalities for ITP were observed in all three patients with transient or partial response. The importance of recognizing the immune mediated thrombocytopenia in patients with myeloma and the implications of this combination are discussed.

Keywords Immune thrombocytopenia, multiple myeloma, IVIg, splenectomy

Case 1

A 49-year-old man presented in November 1996 with severe epistaxis, which had been ongoing for several days. On examination he was anaemic and in addition had extensive superficial bruises and petechial haemorrhages. Investigation results were: Hb 5.9 g/dl; WBC 14.3 $\times 10^9$/l and platelets 21 $\times 10^9$/l. A coagulation screen was normal, as were urea and electrolytes, serum calcium and liver function tests. A blood film examination confirmed thrombocytopenia and neutrophilia and also showed prominent rouleaux formation. Occasional Howell–Jolly bodies were seen; the patient had had a splenectomy following blunt abdominal trauma 30 years previously.

A bone marrow aspirate showed abundant megakaryocytes in all stages of maturation, consistent with a diagnosis of peripheral destruction of platelets as seen in Immune Thrombocytopenic Purpura (ITP). There were also clusters of abnormal plasma cells, comprising about 20% of nucleated cells. Many of these plasma cells showed morphological abnormalities such as bilobed and trilobed forms with abundant cytoplasm. Further investigations revealed immuneparesis and a monoclonal paraprotein band on protein electrophoresis, characterized as IgG lambda and quantified at 40 g/l. Urine studies showed a lambda light chain proteinuria. No osteolytic lesions were seen on skeletal survey. A CT scan of his abdomen showed a small nodule of tissue in left upper hypochondrium, which was thought likely to be accessory spleen. A diagnosis of multiple myeloma and associated immune thrombocytopenia was made.

Because of the bone marrow appearances and the possibility that thrombocytopenia could be due to peripheral destruction, he was given a trial of intravenous immunoglobulin (IVIg) in a dose of 1.0 g/kg body weight by infusion over eight hours, before commencing specific cytotoxic chemotherapy for his myeloma. His platelet count rose to 100 $\times 10^9$/l in a manner similar to that seen in patients with ITP. He was subsequently started on the VAD (vincristine, adriamycin and dexamethasone) regime for his myeloma (Lokhorst *et al.* 1989). Early in his clinical course, he became thrombocytopenic on several occasions but responded each time to infusions of IVIg. A response was also seen immediately following subsequent cytotoxic courses but as with IVIg, these were

Accepted for publication 19 May 2000
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short-lived (Figure 1). He completed six cycles of VAD chemotherapy and clinical review showed that he had responded satisfactorily to his chemotherapy with a drop in his paraprotein load to 10 g/l. His urine was now negative for lambda light chains. In view of this encouraging response and his relatively young age, high dose chemotherapy with rescue peripheral blood stem cell autograft was planned. Unfortunately, he developed an infection 4 weeks after cessation of treatment and died shortly thereafter of overwhelming sepsis.

Case 2

A 36-year-old male presented in 1985 with spontaneous bruising and epistaxis and was found to have a platelet count of 5×10^9/l. A bone marrow examination showed increased megakaryocytes consistent with ITP. There was no excess of plasma cells noted. During the course of routine investigations, an IgG kappa monoclonal band was detected on protein electrophoresis and paraprotein was quantified at 25.8 g/l. There was no associated immuneparesis and no osteolytic lesions were demonstrated.

Prednisolone therapy resulted in partial remission of the ITP. On four occasions, infusions of IVIg (0.4 g/kg body weight daily × 5 days) were associated with good but transient incremental platelet counts in excess of 100×10^9/l. IgG paraprotein levels increased to 54.7 g/l over the course of the next year, but no immuneparesis was documented. In view of the short-lived remissions to steroids and IVIg, splenectomy was undertaken in 1986 as a preparation for likely chemotherapy in the future. This was performed 15 months after presentation following which he maintained his platelet count at about 80×10^9/l. His myeloma continued to progress and his paraprotein levels increased rapidly to 119 g/l, with concomitant immuneparesis of IgA and IgM levels. He also developed renal impairment. A bone marrow examination now showed extensive infiltration with abnormal plasma cells and Bence–Jones proteinuria was detected. Chemotherapy was commenced with VAD (vincristine, adriamycin and dexamethasone) regime and after eight courses paraprotein levels fell to 27.1 g/l. A bone marrow aspirate was performed post chemotherapy when his platelet counts were 15×10^9/l. This showed a significant reduction of plasma cells, but in addition numerous megakaryocytes consistent with peripheral destruction of platelets. No IVIg was given whilst undergoing chemotherapy for myeloma, but during 10 months of treatment it was noted that platelet counts rose following each course of chemotherapy, probably in response to the

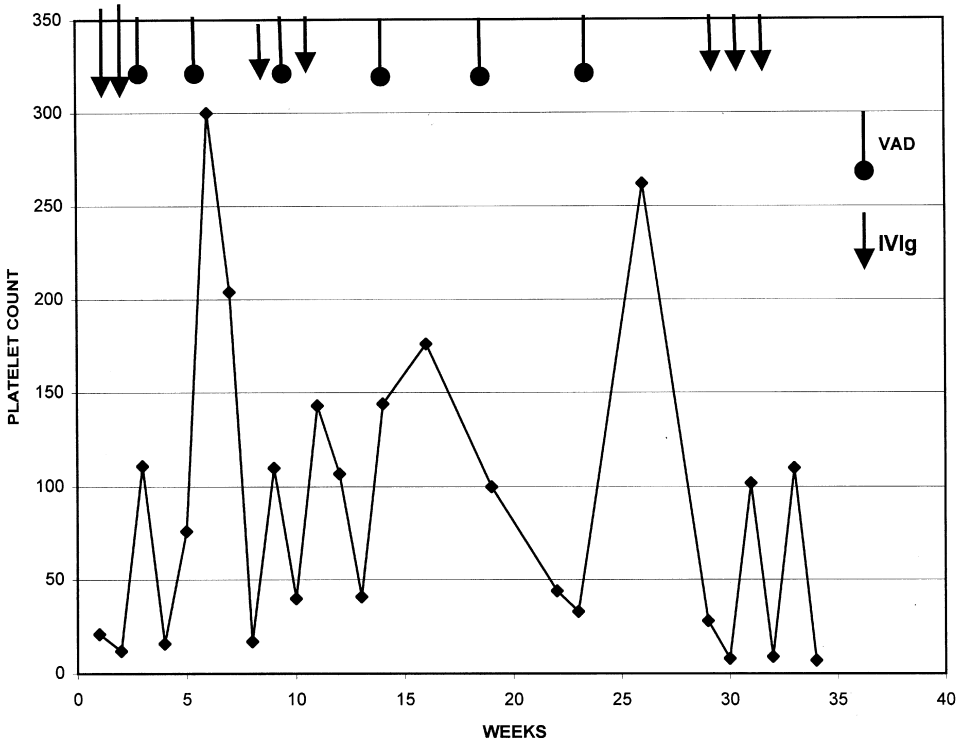

Figure 1. Platelet counts in response to IVIg and VAD (case 1).

dexamethasone and vincristine in the cytotoxic regime. Future chemotherapy was given but during the 10th course of VAD he developed septicaemia and died.

Case 3

A 45-year-old lady was found to be severely thrombocytopenic in 1992 with a platelet count of 20×10^9/l whilst being investigated for menorrhagia. Further investigation included bone marrow examination which was consistent with ITP, but also showed increased number of plasma cells. A small IgG lambda paraprotein band was demonstrated on protein electrophoresis. Serum IgA and IgM levels were low suggesting moderate immuneparesis. No skeletal lesions were seen on radiography.

Her ITP proved refractory to initial steroid therapy and she proceeded to splenectomy. Before splenectomy she received IVIg (0.4 g/kg body weight daily × 5 days) to which she had an excellent platelet increment which was short lived post operatively. She did not respond to steroids and subsequently received IVIg prior to a hysterectomy and to dental extractions and on each occasion her platelets responded satisfactorily. IVIg was used thereafter whenever she became severely thrombocytopenic or symptomatic from her low platelet counts. Her paraprotein levels increased gradually over the next 5 years. In 1997 she was complaining of hip pain and reassessment showed elevated IgG paraprotein levels to 61.0 g/l with significant immuneparesis and Bence–Jones proteinuria. No lytic skeletal lesions were seen. A bone marrow aspirate showed a marked increase of abnormal plasma cells. Oral chemotherapy with CIDEX (lomustine, idarubicin and dexamethasone) was given following which paraprotein levels reached plateau at 36 g/l (Samson 1996). She remains thrombocytopenic however, and she requires IVIg at 2–3 weekly intervals to which she responds and maintains a safe platelet count.

Discussion

Thrombocytopenia is seen frequently in patients with multiple myeloma when most often the aetiology is either chemotherapy induced marrow suppression or bone marrow replacement by myeloma cells. A shortened platelet half-life has also been shown in patients with myeloma (Fritz *et al.* 1986) although no correlation was found between platelet survival and paraprotein concentration. Increased peripheral destruction of platelets may occur either as a result of intrinsic platelet defects such as where a disease associated deviant clone of megakaryocyte produces defective platelets or when extrinsic factors such as paraproteinaemia or raised platelet autoantibody levels increase the susceptibility of platelets to degradation. Elevated platelet associated immunoglobulin has been reported in patients with myeloma and is believed to be secondary to nonspecific binding of serum IgG to platelets (McGrath & Staurt 1979; Hegde *et al.* 1985). Whether this can result in clinically significant thrombocytopenia is debatable.

Immune thrombocytopenia is often seen in patients with lymphoproliferative disorders such as Hodgkin's disease, non-Hodgkin's lymphoma and chronic lymphocytic leukaemia. (Hegde *et al.* 1985; Kuznetsov *et al.* 1992; Lim & Ifthikharuddin 1994). Rather than specific autoantibody being produced by the monoclonal malignant population itself, it is more likely that the inherent immunomodulated state in these diseases allows the emergence of clones that have autoantibody activity. Surprisingly, immune thrombocytopenia has only rarely been documented in patients with multiple myeloma. The paucity of reports may reflect a true rarity of incidence, i.e. if autoantibody is produced at all, elevated myeloma Ig inhibits immune destruction of platelets by causing the same Fc receptor blockade that IVIg does. This however, is unlikely and we believe that this association is simply not recognized often enough. In a literature review, we came across only one case report (Verdirame *et al.* 1985) describing two patients of multiple myeloma and ITP. These were found to be thrombocytopenic during ongoing cytotoxic treatment, one after the second course of chemotherapy and the other after completion of therapy. Both patients were treated with steroids but only went into long-term remission following splenectomy.

Thrombocytopenia was the primary presentation in two of our patients and the diagnosis of myeloma was made at a later stage. A similar clinical evolution is often seen in other lymphoproliferative disorders such as Hodgkin's disease, non-Hodgkin's lymphoma and chronic lymphocytic leukaemia. In one of our patients however, immune thrombocytopenia and advanced myeloma were diagnosed together at presentation. None of our patients at presentation were on any drugs known to cause thrombocytopenia. We felt it important to determine responsiveness to therapeutic IVIg in spite of the coexisting high levels of native IgG paraprotein in this patient because of the potential benefit in later clinical management. It is difficult to determine why exogenous IVIg had a preferential therapeutic effect or indeed how it works at all in the presence of high levels of endogenous IgG. Various mechanisms have been proposed to explain this effect but none is satisfactory. Variations in the properties of these immunoglobulins may be one explanation. Endogenous myeloma

Ig is monoclonal and comprises abnormal whole and fragmented molecules, whereas IVIg is a pooled, polyvalent & polyclonal product (Newland 1988), in addition to which there are difference in IgG subclass distribution. Myeloma protein per se may not have significant binding to reticuloendothelial Fc receptors, which is the most important mechanism to cause elevation of platelet counts. Another possible explanation could be the way IgG is catabolized by FcRn receptors. FcRn are specialized intracellular receptors found in endothelial cells and bind to IgG. Unbound IgG is transferred to lysosomes for degradation. In hypergammaglobulinaemia FcRn receptors are fully saturated which leads on to increased catabolism of endogenous IgG (Yu & Lennon 1999). This IgG depleting mechanism may explain the temporary benefit obtained by exogenous IVIg. Short-lived responses to IVIg were seen in all our patients but it is impressive that this should exercise an effect even after massive dilution in the total body IgG paraprotein seen in myeloma

These cases demonstrate an infrequently reported complication of multiple myeloma, although often seen in other B cell malignancies. It is important to consider immune destruction of platelets when otherwise unexplained thrombocytopenia occurs in myeloma. The specific treatment modalities commonly used in ITP, such as steroids, IVIg or splenectomy may be necessary in these patients and they may further benefit from dexamethasone and vincristine containing regimes in their antimyeloma chemotherapy. Although myeloma is a heterogeneous disease, the clinical presentation of our patients raises the question as to whether they had a different disease from standard myeloma as they were all young and none had bone disease. These cases also highlight the potential risk of sepsis in patients with myeloma who had previously undergone splenectomy. Two of the three patients died of overwhelming sepsis. Underlying immunesuppression due to myeloma compounds the risk of infection with encapsulated organisms in post splenectomy patients (Gowda *et al.* 1995). Therefore a decision regarding splenectomy in myeloma patients should be considered carefully after taking in account various risk factors.

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