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Thrombocytopenia with rituximab treatment—splenomegaly as the risk factor

Jagdish Adiyodi · Jecko Thachil · Stephen Hawkins · Ian Hincks · Barrie E. Woodcock · Rahuman Salim

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Dear Editor,

Anti-CD20 monoclonal antibody (rituximab) is a relatively safe drug with infusion-related reactions being the commonest adverse event. We discuss two cases of thrombocytopenia with its use and propose that splenomegaly is a key predisposing factor.

An 83-year-old woman was diagnosed with hairy-cell leukaemia (HCL) after she presented with anaemia and neutropenia. Computerised tomography (CT) at diagnosis revealed an enlarged spleen (28 cm) with no lymphadenopathy. After 3 years of observation, she was treated with rituximab for B symptoms. Within 24 h of each infusion, she developed thrombocytopenia (range $20\text{--}30 \times 10^9/\text{L}$), although without haemorrhagic manifestations. She achieved remission with four cycles of treatment. A year later, she presented with fatigue and splenic pain. A second identical schedule of rituximab therapy was administered with no infusion-related events. Twelve hours later, she developed pyrexia with platelet count dropping from $74 \times 10^9/\text{L}$ to $22 \times 10^9/\text{L}$ (coagulation screen was normal except for high D-dimer). She developed extensive subdural haematoma and despite platelet transfusions, died the next day.

A 79-year-old lady was diagnosed with marginal zone lymphoma (MZL) during investigation for persistent

lymphocytosis ($15.9 \times 10^9/\text{L}$). After 4 years of regular follow-up for asymptomatic disease, she presented with abdominal distension and worsening lymphocytosis ($36.3 \times 10^9/\text{L}$). CT scan revealed 20 cm splenomegaly. Splenectomy was declined, and instead, chlorambucil and prednisolone were administered. However, 2 months later, she re-presented with dyspnoea and low haemoglobin (8.4 g/L). Haemolysis screen and haematinics were normal although an increase in spleen size (23 cm) was noted. She received standard dose of rituximab with combination chemotherapy and was admitted for observation for minor chills and rigour. The next day, her platelet count dropped from 162 to $43 \times 10^9/\text{L}$ with abnormal coagulation parameters. She was conservatively managed with blood products and achieved complete remission although rituximab was omitted from further cycles.

Rituximab-associated thrombocytopenia is rare with ten previous reports identified in a recent review [1]. The exact mechanism is unclear, while infusion-related cytokine release syndrome (related to complement activation) and heavy bone marrow involvement have been described as key risk factors [1,2]. However, there were no such reactions in the first patient, and not all patients who suffer these reactions develop thrombocytopenia. Also, rituximab-related thrombocytopenia has been reported with autoimmune haemolytic anaemia (AIHA), where bone marrow infiltration with neoplastic cells is unlikely [3].

Another common feature in the reported cases is splenomegaly [1]. Splenic architectural alterations with a predominant red-pulp involvement can possibly explain the acute thrombocytopenia with anti-CD20 therapy. In HCL, homogenous red-pulp expansion with obliteration of the white pulp is characteristic. The red pulp of the spleen consists of Billroth cords and the vascular sinuses, with endothelial lining with hairy-cells extending between these

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sinus endothelial cells [4]. Rituximab removes the CD20-positive hairy-cells and exposes the splenic sub-endothelium. This would trigger platelet activation and aggregation, as with vascular endothelial injury, leading to transient acute thrombocytopenia, which can recover with endothelial repair. This hypothesis of endothelial injury also supports the very high D-dimers and coagulation disturbance, which may be observed in this clinical situation.

The destruction of high CD20-expressing cells in the red pulp can occur in other conditions where rituximab-associated thrombocytopenia has been reported, similar to HCL [1]. Mantle-cell lymphoma predominantly affects the white pulp of the spleen, although rapid turnover causes tumour cells to extend into the red pulp [5]. Two cases of splenic MZL with red-pulp involvement have been reported previously though in our patient, a splenectomy was not undertaken to identify a similar picture [6,7]. Interestingly, morphometric studies on patients with AIHA also showed increased amounts of red pulp [8].

In summary, physicians should exercise caution with rituximab use in patients with splenomegaly, for severe thrombocytopenia can occur with fatal consequences.

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