CASE REPORT

Thrombocytopenia and fever: not just another infection...

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SUMMARY

Diffuse large B-cell lymphoma (DLBCL) is a high-grade, aggressive disease that typically presents with widespread lymphadenopathy and active 'B' symptoms, making it easy to recognise and manage. However, a small proportion of patients can present with no evidence of lymphadenopathy or organomegaly, with the disease confined to the bone marrow; this presentation is also known as 'Primary Bone Marrow DLBCL'. Subsequently, diagnosis can be a challenge, resulting in delayed treatment and an overall poorer prognosis. Given the rarity of this disease, we wished to describe a patient who presented initially with fevers associated with isolated thrombocytopenia and was later diagnosed with this condition. Unfortunately, due to the aggressive nature of this disease, subsequent treatment was unsuccessful. Overall, we felt that in future cases of fevers with thrombocytopenia, clinicians should include this rare lymphoma subtype as part of the differential diagnosis, as early identification and treatment can be associated with a favourable outcome.

BACKGROUND

Secondary bone marrow involvement of non-Hodgkin's lymphoma (NHL) is relatively common, but primary isolated bone marrow involvement in NHL is rare. Primary bone marrow DLBCL (PBM DLBCL) itself has been reported in fewer than 100 documented cases in the past 35 years; however, though the literature on this rare subtype of DLBCL is scarce, it should be highlighted due to the difficulty in forming a timely diagnosis and the aggressive nature of the disease.

CASE PRESENTATION

We report a case of a previously fit and well 69-year-old Caucasian man from the UK who presented to the emergency department, with a 2-week history of fevers and sweats associated with general malaise and dry cough. He had neither urinary nor gastrointestinal symptoms, and had not experienced weight loss. The patient's medical history included hypertension and hypercholesterolaemia, and current medications included amlodipine and simvastatin; he had no known drug allergies.

The patient had one brother who had died in his 60s from myocardial infarction, and parents who had both suffered with hypertension. He had one son, who was well.

The patient was a non-smoker and denied excess alcohol intake. On further questioning, he had not

recently travelled abroad and had no risk factors for exposure to HIV or hepatitis.

On examination, the patient looked generally unwell. He was tachycardic with a regular heart rate of 110 bpm and hypertensive with blood pressure 140/90 mm Hg. He had been feverish in the ambulance, with a temperature of 38.4°C. Examination was unremarkable, with no focal signs in the chest or in the abdomen. Furthermore, there was no palpable lymphadenopathy nor were there any visible rashes.

INVESTIGATIONS

On the day of admission, the patient had isolated thrombocytopenia with platelet count $21 \times 10^9/L$ and normal haemoglobin (130 g/L) and white cell count ($6.5 \times 10^9/L$). The mean corpuscular volume (MCV) was within normal range, measuring 90 fL with normal monocyte and neutrophil counts observed ($1.2 \times 10^9/L$ and $3.6 \times 10^9/L$, respectively). The renal (sodium 135 mmol/L, potassium 4.5 mmol/L, urea 5.0 mmol/L, creatinine 90 $\mu\text{mol/L}$, urate 350 $\mu\text{mol/L}$), liver (bilirubin 8 $\mu\text{mol/L}$, alanine aminotransferase 20 U/L, aspartate aminotransferase 15 U/L) and bone profiles (calcium 2.25 mmol/L, phosphate 1.3 mmol/L) were entirely normal. The patient had a markedly elevated C reactive protein (CRP) level measuring 150 U/L, suggestive of an underlying infective or inflammatory process.

Given the thrombocytopenia and general symptoms, a full clotting screen was sent to rule out disseminated intravascular coagulation (DIC), a potential complication of overwhelming infection. This was normal and included prothrombin time (13.2 s), activated partial thromboplastin time (30 s), fibrinogen (3.5 g/L) and fibrin degradation products (8 mg/L). Lactate dehydrogenase (LDH) level was also checked. This was markedly elevated at 3734 U/L and therefore we proceeded to have a blood film examined on the day of admission. This showed no evidence of thrombotic thrombocytopenia purpura and, given that the patient lacked other clinical features associated with this condition, including renal impairment and neurological compromise, an ADAMTS13 level was not requested. Additionally, the red and white cells displayed no dysplastic morphological features and no malignant cells were seen.

Given that no obvious haematological cause could be identified, the patient had a full septic screen including blood cultures, urine cultures and chest X-ray, which were entirely normal. In spite of this, however, the patient was started on broad-spectrum antibiotics (tazosin and gentamicin).

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By day 2 of admission, the patient continued to have temperature spikes and his liver function started to become deranged, with rising ALT (100 U/L) and bilirubin (56 μ mol/L) associated with ongoing thrombocytopenia (15×10^9 /L). At this point, a viral screen was sent to exclude this as a potential cause for his symptoms and thrombocytopenia. This included PCR levels of hepatitis B, hepatitis C, cytomegalovirus, Epstein-Barr virus and HIV, all of which were negative. In addition to this, we sent a vasculitis screen, which included antineutrophil cytoplasmic antibody (ANCA), antinuclear antibody (ANA) and erythrocyte sedimentation rate (ESR). ANCA and ANA were both negative although the ESR, unsurprisingly, was elevated at 79 U/L.

By day 3 of admission, the patient continued to deteriorate, showing features consistent with overwhelming sepsis, including persistent tachycardia (heart rate between 130 and 150 bpm), temperature spikes (ranging between 38.4 and 39.6°C) and hypotension (systolic blood pressure between 95 and 100 mm Hg). Furthermore, he had now developed a pancytopenia with haemoglobin 75 g/L, white cell count 1.5×10^9 /L, neutrophils 0.7×10^9 /L and platelets 10×10^9 /L (MCV remained normal at 96 fL). Notably, his renal and bone profile continued to remain normal (urea 9 mmol/L, creatinine 100 μ mol/L, urate 375 μ mol/L, calcium 2.39 mmol/L and phosphate 1.29 mmol/L) excluding tumour lysis syndrome. He proceeded to have a full body CT scan to rule out potential lymphoma or other non-haematological malignancies. The scan was entirely normal with no evidence of infection nor occult malignancy. Additionally, the lymph node and spleen size were notably within normal range.

Given that the patient was now pancytopenic, a bone marrow biopsy was performed on day 4 of admission—the procedure was complicated as there was no aspirate, that is, it was a ‘dry tap’, and only a trephine sample was obtained. The histopathologists confirmed the diagnosis of PBM DLBCL, 1 week later (figure 1).

DIFFERENTIAL DIAGNOSIS

PBM DLBCL is a histological diagnosis. Usually, patients with DLBCL present with widespread lymphadenopathy and hepatosplenomegaly, which is confirmed through both clinical examination and imaging. This patient had a normal clinical examination and CT of the full body was unremarkable.

From initial presentation, infection was considered the likely cause and thus a septic screen, including virology, was sent to

rule these out. The patient had had no recent foreign travel, but if this had not been the case, then we would have also screened for malaria and dengue fever.

Patients who present with overwhelming sepsis can be at increased risk of DIC, which is typically associated with thrombocytopenia, although our patient had a normal clotting screen.

We lastly considered haematological causes for this presentation, as the initial blood film was normal with no evidence of TTP nor of any malignancy. When the patient became pancytopenic and had a normal CT scan, we then proceeded to bone marrow biopsy to complete the investigations, which, finally, confirmed the diagnosis.

TREATMENT

The patient unfortunately deteriorated rapidly and was admitted to intensive care by day 7 of admission. At this point the blood counts had deteriorated significantly (haemoglobin 60 g/L, white cell count 1.0×10^9 /L, neutrophils 0.3×10^9 /L and platelets 5×10^9 /L), and the patient had multiorgan failure. For patients with DLBCL, the standard chemotherapy combination regimen consists of rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CHOP). However, given the renal impairment, the cyclophosphamide and doxorubicin, in particular, had to be dose adjusted. This treatment regimen is generally well tolerated with few adverse events reported. Furthermore, a recent meta-analysis has shown this regimen to be superior to CHOP alone in patients with DLBCL, with lower relapse rates and improved overall survival.¹

Usually patients with DLBCL are assessed using a combination of clinical examination and imaging to review the lymph node and organ size. However, primary bone marrow DLBCL can be more challenging and, often, clinicians use the full blood count and LDH to monitor response, with a bone marrow biopsy after six cycles of therapy to reassess disease.

OUTCOME AND FOLLOW-UP

Our patient received the first cycle of R-CHOP with appropriate dose adjustments. However, he made little improvement following this with on-going organ support and no improvement in the blood counts. Given the lack of progress, we had a lengthy discussion with the family and it was agreed that we would palliate. The patient unfortunately passed away 7 days after the diagnosis was made.

DISCUSSION

PBM DLBCL can be challenging, as was demonstrated by this patient, with non-specific presenting symptoms. The differential diagnosis often includes infection and, subsequently, patients are managed with multiple antimicrobials before further investigation is considered. Hence the diagnosis of this rare lymphoma subtype is often delayed, resulting in poorer outcomes, with a median 5-year survival rate of around 30% reported.²⁻⁴

As mentioned, the secondary involvement of lymphomas in the bone marrow is common whereas PBM DLBCL is rare. It currently accounts for 1.16% of lymphomas and 2.65% of DLBCLs.² In the largest case series, Kajiura *et al* reported 37 patients over three decades who had clinical presentation similar to our case, with non-specific symptoms including fatigue, weight loss and fevers. Raised LDH was a near-universal finding and patients often had advanced disease at presentation.³

In 2011, Chang *et al*⁴ proposed the following diagnostic criteria for PBM DLBCL:

Figure 1 Bone marrow biopsies confirming the presence of abnormal, large-sized lymphoid cells with features characteristic of diffuse large B-cell Lymphoma (left side). These were strongly CD20 positive on immunohistochemistry staining (right side). Images were provided courtesy of Dr Simon O'Connor, Consultant Histopathologist, Royal Marsden Hospital, Sutton.

1. Pathologically confirmed bone marrow involvement with diffuse large cell lymphoma.
2. Expression of pan-B cell markers, CD19 or CD20, shown by immunohistochemical stain or flow cytometry analysis.
3. Absence of lymph node involvement, defined as any lymphadenopathy >1 cm in size shown by whole body CT scan or physical examination.

It should be noted that, in addition to the above, patients are often pancytopenic at presentation, making them prone to infection and bleeding complications.⁴⁻⁷ Our patient was unusual as he initially presented with isolated thrombocytopenia, and this has only been reported in one other case, where the patient had immune-mediated thrombocytopenia (ITP) associated with lymphoma.⁸

As previously mentioned, patients often have advanced disease due to delay in clinical presentation and subsequent diagnosis. Though the use of bone marrow biopsy is included as one of the major diagnostic criteria for PBM DLBCL, this procedure can have its own limitations. This was demonstrated by our patient, where no aspirate was obtained, resulting in a further delay of the diagnosis as we were awaiting immunohistochemistry staining from the histopathologists. To avoid this, some authors have suggested the use of fluorodeoxyglucose-positron emission tomography (FDG-PET) scan to identify the diagnosis more rapidly.⁹ Lapa *et al*⁹ described a case of PBM DLBCL, affecting the distal legs in a patient who had persistent B symptoms, which was only identified using PET scan, after two bone marrow biopsies were negative. Additionally, Cortes-Romera *et al*¹⁰ compared FDG-PET against bone marrow biopsy in 147 patients with lymphoma, with 14% displaying discordant features where bone marrow biopsy was negative but FDG-PET scan was positive. Hence, this group concluded that FDG-PET imaging is a non-invasive technique that is far more sensitive for the detection of bone marrow involvement in lymphoma cases in comparison with bone marrow biopsies. Regarding our own patient, a FDG-PET scan was considered, but this would have had to be performed at another hospital, and the patient was considered too clinically unstable for transfer. However, if this imaging had been performed, it is likely that we would have identified the diagnosis much sooner.

The standard chemotherapy regimen usually includes a combination of rituximab with CHOP or other forms of cytotoxics.³⁻⁷ The addition of rituximab has been shown to play a critical role in the management of these patients, as Chang *et al*⁴ demonstrated, where superior response and survival rates were seen in patients treated with R-CHOP in comparison to CHOP alone. In 2012, Kazama *et al*¹¹ described a patient who remained disease-free 7 years after successful treatment with R-CHOP followed by autologous stem cell transplant (ASCT). The use of upfront ASCT is controversial for patients with PBM DLBCL due to the rarity of this disease and concerns that the autograft may become contaminated causing early relapse. However, Kazama *et al*, interestingly, included rituximab in their conditioning regime, which may have prevented the latter complication. As mentioned earlier, rituximab has demonstrated a major role in the initial management of this lymphoma subtype and, therefore, it is somewhat unsurprising that this agent was effective in the transplant setting. However, this is a single case report and further data are required from a larger cohort of patients.

In conclusion, the key management of PBM DLBCL is early identification using the diagnostic criteria as described earlier. However, if there is any doubt regarding the bone marrow biopsy technique, PET imaging should also be employed, as this has demonstrated greater sensitivity for the detection of this particular lymphoma subtype. Once confirmed, a rituximab-

based combination chemotherapy regimen should be used as initial induction.⁴ Depending on patients' performance status, they should consequently be considered for upfront autologous stem cell transplant, as this has been associated with long-term remission and prolonged survival.¹¹

Learning points

- ▶ Primary bone marrow diffuse large B-cell lymphoma (PBM DLBCL) is characterised by pancytopenia and absence of lymphadenopathy.
- ▶ PBM DLBCL should be part of the differential diagnosis in patients presenting with fever associated with cytopenias and high lactate dehydrogenase.
- ▶ Initial investigations should rapidly exclude infection (bacterial, viral and parasite) and vasculitis. Additionally, all patients should have their clotting checked to exclude disseminated intravascular coagulation as part of the diagnostic work up.
- ▶ Clinical suspicion and the early initiation of intensive chemotherapy, followed by potential autologous stem cell transplant, are likely to lead to improved clinical outcome and prolonged survival.⁸

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