CASE REPORT

Splenomegaly in the returning traveller: a diagnostic workup

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SUMMARY

Isolated splenomegaly is an unusual condition encompassing a broad range of diagnoses. We report a case of a 38-year-old Asian man who presented with insidious abdominal discomfort and night sweats following recent travel to India. Massive splenomegaly was the only prominent feature on clinical examination and on subsequent imaging. Extensive investigations were performed, ultimately resulting in transfer to a tertiary centre for definitive diagnosis via a splenic biopsy. A fine-needle aspiration was performed, and revealed diffuse large B-cell lymphoma (DLBCL). Consequently, he was successfully treated with a course of chemotherapy.

BACKGROUND

Presenting solely with splenomegaly is unusual and can largely be attributed to either malignancy or infectious disease. Thorough clinical examination and investigations will generally determine the cause.¹ However, in this case, extensive investigations were performed with minimum yield. In the absence of another histopathological source a splenic biopsy was successfully performed. This case illustrates two main points. First, where clinical suspicion for malignancy is strong; investigations should be used effectively to exclude this diagnosis, prior to performing extensive and largely unnecessary tests. Second, splenic biopsies are an undervalued resource with a good yield and safety profile; thus, should be considered earlier in the diagnostic process.²

CASE PRESENTATION

A 38-year-old Asian man, who was otherwise well aside from controlled asthma and β -thalassaemia trait, had been visiting family in a rural farming village in Punjab for 1 week. On return he had felt insidiously unwell some months later. He presented to hospital with 2 months of intermittent left upper quadrant pain, fatigue, low-grade fever and night sweats. He was exposed to one relative with tuberculosis (TB) during his visit to India. However, he denied any other known infected contacts, insect bites, had not been swimming abroad or exposed to any other infections. There was no significant family history, alcohol misuse, weight loss or trauma. On examination there was marked splenomegaly, 10 cm below the costal margin, but no palpable lymphadenopathy or other abnormalities. An ultrasound (US) scan confirmed this and he was admitted for further investigations.

INVESTIGATIONS

A CT scan of the chest, abdomen and pelvis was performed (figure 1). This revealed massive splenomegaly (18.5 cm diameter), containing a large heterogeneous mass with multiple areas of necrosis (figure 2). No other abnormalities were identified other than adenopathy at the splenic hilum.

Routine blood tests were within normal range, bar a stable microcytic anaemia, consistent with known β -thalassaemia trait. C reactive protein and lactate dehydrogenase (LDH) were both elevated at 70 mg/L and 1010 IU/L, respectively. An extensive infection screen was performed including: parasitic, mycobacterial and fungal screens, as well as, an immunosuppressive panel, including HIV and viral hepatitis. These were all negative. Further tests confirmed past exposure to Epstein-Barr virus, varicella zoster, herpes simplex virus, cytomegalovirus, and hepatitis A. Repeated blood films and cultures excluded malaria or other pathogens. An auto-immune screen, tumour markers and ACE inhibitors all proved negative. Serum protein electrophoresis was normal and immunoglobulin screen revealed β -2 microglobulin.

Bone marrows aspirate and trephine biopsy revealed normal cellularity and megakaryopoiesis with no evidence of lymphoproliferative or myeloproliferative disease or leishmaniasis.

The patient remained afebrile but his symptoms persisted. After much discussion, he was transferred to a tertiary infectious diseases centre for a splenic biopsy. Ultimately US-guided splenic fine-needle aspiration was performed (figure 3). The histology and immunohistochemistry was consistent with a diffuse large B-cell lymphoma (DLBCL) (positive for: CD20, CD79a, Oct2, BCL2, BCL6, MUM1 (+), CD30 (+); 90% proliferative index as assessed by ki-67 staining).

DIFFERENTIAL DIAGNOSIS

Given the insidious onset and massive splenomegaly a lymphoproliferative cause was suspected and haematological advice was sought. The elevated LDH and presence of β -2-microglobulin supported this, despite negative bone marrow and absence of significant lymphadenopathy. Haematological disease is certainly the most common, encompassing 16–66% of all causes of splenomegaly.¹ Of these, the most common is lymphoma, accounting for 15–44% of cases. As this is a sinister differential with significant consequences, this needs early exclusion. Therefore, if serum and bone-marrow investigations prove negative or inconclusive,

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Figure 1 Admission CT scan showing splenomegaly and a heterogeneous mass.

splenic biopsy or splenectomy should be considered for tissue diagnosis.

However, given the TB contact and travel history, the haematologists were keen to exclude infection and did not feel malignancy was likely. The CT scan appearances could be consistent with splenic abscesses, for which major infectious differentials include: malaria, TB, amoebic or hydatid disease. Abscesses have been reported with these pathogens, and these pathogens are prevalent in India.^{1 3–6} However, the patient did not demonstrate any features of severe sepsis and infection markers remained only moderately elevated throughout the admission. Further history of hepatic and gastrointestinal disease did not aid investigations, but it is important to elicit these when considering infection.¹ Regarding splenic infections, US and CT are invaluable, as TB and hydatid disease can reveal specific patterns

Figure 2 Marked splenomegaly with an approximate splenic diameter of 18.5 cm and a large heterogeneous mass containing areas of necrosis.

Figure 3 H&E staining of splenic biopsy: depicting multiple abnormal cells, enlarged lymphocytes, prominent nuclei, excess cytoplasm and CD20 positivity (arrow depicting example of abnormal cell), 400× magnification.

of lymphadenopathy or cystic disease, thus, narrowing the differentials. Furthermore, bone marrow biopsy is a useful second-line investigation as it can help differentiate between TB and haematological malignancies. Unfortunately, in this case they offered no additional benefit to the isolated splenomegaly. Ultimately, biopsies can be performed; however, precautions must be taken to prevent infection dissemination.

There were no further clinical features of systemic diseases such as sarcoidosis, amyloidosis or vascular abnormalities to guide an alternative diagnosis. Therefore, transfer was arranged to an infectious disease unit for tissue diagnosis via splenic biopsy.

TREATMENT

Post biopsy the patient was referred to the lymphoma team, 2 months after initial presentation, where he was started on RCHOP chemotherapy (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone). He successfully completed six cycles of chemotherapy before achieving remission.

OUTCOME AND FOLLOW-UP

He had a good response to six cycles of R-CHOP 21 chemotherapy and was in complete metabolic remission on his FDG PET and CT scans 8 months following the initial presentation. There was a significant reduction in splenic size from 14.3×8.3×18.9 cm to 6×3.6 cm with no associated lymphadenopathy or bone disease following therapy. He continues to be reviewed every 3 months.

DISCUSSION

An extensive array of diseases can be associated with splenomegaly.¹ In cases of isolated splenomegaly, detailed history, examination and appropriate investigations are essential to exclude a systemic illness.² The most common causes of isolated splenomegaly are haematological: 25–66%, hepatic: 12–46%, infective: 13–25%, primary splenic: 25% and others: 8–21%.¹ β -thalassaemia trait may be associated with mild splenomegaly although not to a palpable degree and certainly, where

significant, should prompt investigations seeking an alternative diagnosis.^{1–6} However, in cases of massive splenomegaly, defined by a spleen palpable more than 8 cm below the costal margin or weighing >1000 g, the differential diagnosis is further restricted. In the majority of cases the cause will be haematological in aetiology that is, lymphoma or myeloproliferative disease, but may be secondary to infections, including malaria, leishmaniasis, and schistosomiasis. Rarer causes such as sarcoidosis or Gaucher's disease can be considered if the above are excluded.¹

In our case, after discussion with haematology, it was felt that the travel history and CT findings of a focal mass with necrosis necessitated the exclusion of an infective aetiology. Splenic abscesses are a rare finding (0.05–0.7% frequency) but are associated with significant mortality. They have bacterial, parasitic and fungal aetiologies and most commonly result from haematogenous spread from an infective sources, with aerobes accounting for most cases.^{1–6} Infective endocarditis has also been implicated with a reported incidence of 10–20% of associated splenic abscess.

The insidious onset of symptoms in this case and presence of elevated LDH raised early suspicion of lymphoproliferative disease. The spleen is a common site of lymphoma dissemination and may be involved with any lymphoid malignancy. However, primary splenic lymphoma represents a rare diagnosis.² According to some authors it accounts for <1% of incidences, as it is strictly defined by involvement of only the spleen and splenic hilar lymph nodes, in the absence of any other localised tumours.⁷ Several subtypes of lymphoma have been described including DLBCL, mantle cell lymphoma, hairy cell leukaemia, splenic marginal zone lymphoma, prolymphocytic leukaemia, chronic lymphocytic leukaemia, and Waldenström macroglobulinaemia.⁸

Ultimately in cases of primary splenic lymphoma the main treatment options available include splenectomy, chemotherapy, biologicals or a combination of the aforementioned therapies.⁹ Splenectomies are generally perceived to be safe, effective and reduce symptom burden.¹⁰ However, improved median survival is only seen in certain subtypes including Lymphoplasmacytic, follicular, marginal-zone and mantle-cell lymphomas. For all other subtypes, as in our case of DLBCL, chemotherapy is preferred. Some studies do suggest splenectomy is preferable but there is little literature available post-Rituximab era. These studies suggest that splenectomy should be used in early primary splenomegaly DLBC. However, the authors also note that 94% of their patients had chemotherapy in the splenectomy and non-splenectomy group. This bodes the question if chemotherapy is to be used in addition to splenectomy, what is the additional benefit of splenectomy. The authors also advise splenectomy should not be routinely performed for a diagnosis, as biopsies are preferred given the lower risk of morbidity and mortality. In our case as infection could not be excluded; a biopsy was preferable compared with splenectomy if infection was present. Where infection is present, splenectomy could result in pathogen translocation and removal of an otherwise normal spleen.

Furthermore, the high diagnostic yield from peripheral blood sampling and bone marrow examination suggests that a thorough haematological assessment should always precede a diagnostic splenectomy.¹¹ Finally, CTs are an essential investigation to elucidate the cause of splenomegaly and, where present, aids in the staging process for malignancy. In a recent case series examining the radiographic findings of primary splenic lymphomas Li *et al*⁸ report DLBCL as being the most frequent histological subtype. Necrosis was observed in 70.6% of all cases and

in 77.8% of DLBCL. However, significant necrosis may occur, and in some cases with single large lesions, may mimic splenic abscess, which again is relevant given the possible infectious differential diagnosis in this patient.^{1 3–6 8}

In most patients with splenic lymphoma evaluation of the bone marrow by a skilled histopathologist will establish the diagnosis and complete the staging process. However, in cases with undetectable malignancy in peripheral blood and bone marrow; but continued suspicion of malignancy, obtaining a histological diagnosis is crucial to ensure timely treatment.^{7–8 12} Typically in patients with evidence of systemic disease or who remain unwell where investigations have not yielded a diagnosis splenectomy may be considered. This has a dual role in establishing the diagnosis and providing therapeutic benefit.⁸ However, for patients with macroscopic splenic nodules in the absence of liver disease and portal hypertension there is increasing evidence for the use of core needle biopsies to obtain the diagnosis.^{2 7 12 13} Historically there has been reluctance in performing splenic biopsy given the perceived risks of major bleeding involved.² However, studies show that the complication rates are significantly reduced when 20–22 Gauge needles are used.^{2 7} A recent meta-analysis showed a major complication rate of only 1.3%. This is comparable to liver and kidney biopsies. Furthermore, diagnostic yield remains high. There are improved diagnostic yields when needles smaller than 18 Gauge are used, but a slight increase in complications.^{2 7 13} A higher false-negative rate is observed in patients with diffuse splenomegaly versus focal lesions suggesting that biopsies should be avoided in this cohort of patients. Given the overall safety and diagnostic yield of splenic biopsies, early consideration of this investigation is warranted to provide a definitive diagnosis and aid timely therapeutic management.

Learning points

- ▶ A detailed travel history is crucial to narrow major differentials, thus preventing diagnostic delays and misuse of resources, and where malignancy is suspected this should be excluded first.
- ▶ Splenic biopsies should be considered earlier in the diagnostic process of isolated splenomegaly, to differentiate between infection and malignancy, as they have good diagnostic yield and safety profiles.
- ▶ Management of diffuse large B-cell lymphoma (DLBCL) depends on its staging. In the context of isolated splenomegaly, with DLBCL, as there are often malignant cells outside the spleen, chemotherapy is preferred. However, splenectomy can be considered in adjunct, but not routinely given the associated morbidity.

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Contributors PUP performed a literature search, designed, drafted and was involved in the revision of the case report. PS facilitated the literature search alongside MJ and both helped to revise the final draft.

Competing interests None declared.

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