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Going with the flow – diagnosing a lymphocyte rich pleural effusion

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Dr Catherine Hyams (CH), Respiratory Registrar:

Presentation to Pleural Clinic

A 52-year old Medical Secretary was seen in Pleural Outpatient Clinic as follow-up after hospital discharge from the Surgical team 3 weeks previously. Since discharge, the patient had progressive breathlessness with an exercise tolerance of 10 metres (previously unlimited) and noted a mild dry cough. She was a lifelong non-smoker. Fevers, sweats or weight loss were not reported. She had no relevant medical or travel history, with no known exposure to asbestos or other chemical agents. Clinical examination was consistent with a large left-sided pleural effusion, which was confirmed on chest radiograph (Figure 1A) and thoracic ultrasound. The chest radiograph also demonstrated infiltrates in the left upper zone.

Previous Surgical History

The patient originally presented with abdominal pain and non-bloody diarrhoea 4 months prior to her clinic appointment. Routine blood tests were unremarkable, and she was diagnosed with probable infective colitis. She was discharged home with a plan for outpatient colonoscopy if her symptoms continued. Two months following this, the patient represented to the surgical team; however, her pain was now epigastric. An abdominal ultrasound was unremarkable, and she was discharged home and her colonoscopy expedited.

The patient was readmitted 48 hours following this second discharge, and was haemodynamically unstable with an acute abdomen. Blood tests revealed an acute fall in haemoglobin (77g/L from 134g/L; normal range 12.0 to 15.5 g/L) with normal platelets (365 x 10^9/L) and slightly elevated white cell count (15.2 x 10^9/L; normal range 4.5 to 11.0 × 10^9/L). Cross-sectional imaging demonstrated acute splenic rupture and haemoperitoneum (Figure 1B). An emergency splenectomy was performed, during which spleen and liver biopsy samples were sent for histology. The patient stabilised but had ongoing fevers post-operatively. A chest radiograph performed at this time revealed

a left-sided pleural effusion, and she received Tazobactam-Pipercillin covering possible pleural infection. A total of 1400mL pleural fluid was aspirated and confirmed exudative under Light's criteria (serum protein 73g/L and lactate dehydrogenase (LDH) 377U/L; pleural protein 47g/L, LDH 336U/L and pH 7.32). It was thought the effusion may be reactive to the splenectomy and therefore likely self-resolving, however follow-up with the pleural service was arranged.

Review of Existing Investigations in Pleural Clinic

Before being seen in pleural clinic, further results of the patient's pleural fluid analysis became available – cytological examination did not reveal malignant cells and cell-differential confirmed a lymphocytic effusion (75% lymphocytes, 20% polymorphs, 5% mesothelial cells/monocytes). The splenic biopsies revealed large non-caseating granulomas with no evidence of malignancy (Figure 1C). In addition, the liver Tru-cut® biopsies also showed non-caseating granulomas and lymphocytes in the portal tract.

Professor Nick Maskell (NAM), Consultant Respiratory Physician:

When reviewing the cross-sectional imaging taken during the patient's acute surgical admission, it became apparent that a small pleural effusion was present before splenectomy (Figure 1D). The lymphocyte-rich effusion was unlikely attributable to acute bacterial infection, indicating a more chronic process. Of note the patient's inflammatory markers had also fallen (C-reactive protein (CRP) currently 40mg/L versus 221mg/L at time of aspiration).

There is a wide differential for an exudative lymphocyte rich pleural effusion, with the most common causes listed in the BTS pleural disease guidelines (1), including malignancy, lymphoma, tuberculosis, cardiac failure, post-coronary artery bypass graft and rheumatological disease. It should be noted that most effusions related to cardiac failure are transudative, and those that are exudates are usually either borderline or discordant. The effusion in this case is an unequivocal exudate.

Malignancy (either solid tumour malignancy including melanoma and metastatic adenocarcinoma, or lymphoma) and congestive cardiac failure are the most common aetiologies of a lymphocytic effusion in the UK. The patient's cross-sectional imaging did not reveal evidence of malignancy, and pleural cytology did not detect malignant cells. A repeated pleural aspiration underwent lymphocyte subset analysis, and did not reveal any evidence of lymphoma. Spleen biopsies had a normal distribution of T- and B-cells on histology and CD20 and CD30 stains on the liver biopsy were negative, pointing away from a diagnosis of lymphoma.

In order to fully exclude a malignancy or lymphoma, this patient would need to undergo a medical thoracoscopy, allowing visualisation and appropriate pleural sampling. A medical thoracoscopy would also enable samples to be obtained for TB culture, as standard operating procedures ensure some samples are not preserved in formaldehyde. However the patient was not keen to undergo a thoracoscopy immediately, as she felt she was still recovering from her splenectomy and significant recent hospital admission.

TB pleuritis is an infrequent cause of a lymphocyte-rich effusion in the UK. Pleural fluid adenosine deaminase (pfADA) can be used in populations with low TB prevalence to exclude pleural TB. A prospective trial performed by Arnold *et al* concluded that pfADA <35iU/L has a 99% specificity and 98.9% negative-predictive value in excluding TB in patients with lymphocyte-rich pleural effusions (2). Raised pfADA can be found in empyema, complex parapneumonic effusion and in some cases of malignancy. However, these processes are associated with neutrophil predominance, as opposed to TB in which the effusion is lymphocyte-rich. In the same prospective trial, malignant effusions with high pfADA were found to be neutrophilic, with only a single lymphocyte-predominant false positive found (2).

In this case, pfADA was 20.0IU/L and serum QuantiFERON® was negative, making tuberculosis unlikely. Additionally spleen samples were negative on stain for acid-fast bacilli. Unfortunately samples obtained during surgery were preserved in formaldehyde, making culture unavailable.

CH:

Pleural fluid from repeat thoracentesis was unchanged, demonstrating an ongoing lymphocyte-rich exudative effusion. The pleural fluid did not demonstrate any acid-fast bacilli on smear test, and no mycobacteria were cultured. The patient had an unremarkable echocardiogram, and NT pro-BNP 73.0pg/L, excluding congestive cardiac failure.

Serum angiotensin converting enzyme (ACE) was <3iU/L and corrected calcium was normal. The patient was antinuclear antibody (ANA)-HEp-2 negative, Anti-neutrophil cytoplasm antibodies (ANCA) negative and Rheumatoid Factor 11iU/L (normal range < 14 IU/ml), making autoimmune conditions such as rheumatoid arthritis unlikely. Serological tests suggested previous Epstein Barr virus infection and were negative for toxoplasmosis, aspergillus and histoplasmosis.

The case was discussed during the multi-disciplinary team meeting, aiming to reviewing pathology samples obtained during surgery.

Dr Richard S Daly (RSD), Consultant in Cellular Pathology:

Splenic tissue submitted for histopathological examination contained multiple large geographic necrotising granulomata (Figure 1C). The necrosis was not caseous, but suppurative, comprising necrotic material admixed with neutrophils, forming microabscesses/suppurative granulomata, bordered by a palisaded arrangement of histiocytes, along with some lymphocytes and plasma cells, but with no multinucleated giant cells. Foci of mycobacterial infection almost always include multinucleated giant cells at the edge of the caseation necrosis. No acid-alcohol fast bacilli were identified in Ziehl-Neelsen stained sections of splenic tissue in this case.

Sarcoidosis granulomata are usually non-necrotising, include multinucleated giant cells of both Langhans' and foreign-body types. Necrotising sarcoidosis can occur, but the necrosis in such

cases is not typically suppurative in nature, and granulomata are usually accompanied by an angiitis of small arteries and veins. Vasculitis was not seen here.

A palisaded histiocyte arrangement in granulomata is often seen in (but not limited to) infective granulomata. Fungal infection was considered unlikely, with negative staining for any spores or hyphae in Periodic acid-Schiff (PAS) & Grocott stained sections.

NAM:

Whilst the concurrent finding of granuloma may heighten the clinical suspicion of sarcoidosis, it is extremely rare for sarcoidosis to cause clinically significant pleural effusions. It is therefore unlikely that this large pleural effusion is attributable to sarcoidosis, and we would only revisit sarcoidosis as a diagnosis once all other causes of granulomas with concurrent pleuritis have been excluded.

CH:

Some further serological tests were therefore performed to investigate for causes of granulomatous disease. Rarer causes of a lymphocytic pleural effusion in a patient with granulomatous disease include *Coxiella burnetii*, *Mycoplasma pneumoniae*, *Brucella* species, *Borrelia burgdorferi*, *Yersinia enterocolitica*, *Yersinia pseudotuberculosis* and hepatitis viruses including hepatitis A, B and C.

NAM:

Revisiting the history is always useful, and specifically we need to reconfirm if there is any recent travel history and new drugs that may be responsible, as well as ascertain a detailed history

regarding any pets, hobbies and environmental exposure from home and work. A further clinical examination is also important.

In this case, on further examination it was noted that she had old scratch marks on her forearms and shins. On further questioning, she revealed that she had cats at home, and had acquired a new kitten 2 weeks before her symptoms started. Serology for *Bartonella henselae* was therefore performed using an immunofluorescence assay, and was positive (IgM titre < 1:20, IgG titre > 1:256) confirming a diagnosis of cat-scratch disease.

RSD:

Suppurative granulomata, such as those present in the spleen in this case, are described in well-developed lesions of cat scratch disease.

Dr Megan Jenkins (MJ), Specialist Registrar, and Dr Izak Heys (IH), Consultant in Infectious Diseases

Bartonella henselae is a Gram-negative bacillus recognised as one of several *Bartonella* spp. causing human Bartonellosis (3). These infections range from self-limiting cat-scratch disease (CSD) to life-threatening bacteraemia, endocarditis, vasculitis and bacillary peliosis. *B. henselae* have been identified in cats, dogs, humans and horses transmitted via cat fleas and body lice. A few weeks before this patient's symptoms began, she acquired a new kitten that was prone to excessive scratching. However, not all patients have an exposure history. The classical presentation of CSD is tender lymphadenopathy presenting 1-3 weeks after exposure and potentially lasting for months. Atypical CSD occur in 5-14% of cases (3). Involvement of the lung is recognised but uncommon, and typically develops 1-5 weeks after lymphadenopathy. In a case series of 13 patients with thoracopulmonary manifestations of CSD, 8 had a pleural effusion and 6 had pneumonia (4). Whilst hepatosplenic involvement is well recognised, splenic rupture has been reported in only a few cases (5).

The use of antibiotics to treat CSD is controversial and most *Bartonella* infection cases resolve without treatment (3). However, azithromycin has been shown to decrease lymph node volume more rapidly than placebo. There is no data available on usage of antimicrobials in immunocompetent patients with atypical CSD, although doxycycline, rifampicin, gentamycin and trimethoprim/sulphamethoxazole have been used either alone or in various combinations. In this case, the patient received a 2 week course of doxycycline, after which her symptoms and pleural effusion resolved, as well as the infiltrates previously demonstrated on her chest radiograph (Figure 1E).

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Figure Legends

Figure One:

(A) Chest radiograph on presentation to Respiratory Outpatient Clinic showing moderate left sided pleural effusion and left upper zone infiltrate; (B) Computer Tomography (CT) showing splenic laceration (SL) and haemoperitoneum (HP); (C) H&E stained section (x25 magnification) from the splenectomy specimen, demonstrating large geographic areas of non-caseating suppurative granulomata bordered by a palisaded arrangement of histiocytes (highlighted by arrows) and the notable absence of multinucleated giant cells, with background normal splenic parenchyma occupying the rest of the image; (D) Slice of CT scan demonstrating left-sided pleural effusion; (E) Chest radiograph after treatment, with complete resolution of the pleural effusion and lung infiltrate.