CASE BASED DISCUSSIONS

Case-based discussion from North Tyneside General Hospital: somatostatin analogues in yellow nail syndrome associated with recurrent pleural effusions

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Kristian Brooks (KB): A 77-year-old man presented to accident and emergency with a 1-month history of progressive breathlessness and reduced exercise tolerance. He had no chest pain, cough or wheeze, but had bilateral leg swelling and 4 kg weight loss. He had long-standing nail dystrophy and, following presentation with recurrent lower respiratory tract infections several years previously, bronchiectasis had been confirmed on high-resolution CT. He was a lifelong non-smoker, but had significant occupational asbestos exposure. There was no relevant family history. Chest radiograph showed large bilateral pleural effusions. Blood tests, including markers of infection and inflammation, were unremarkable. An ultrasound-guided pleural tap showed a lymphocytic exudate.

Stephen C Bourke (SCB): The combination of nail dystrophy, lymphocytic pleural effusions, bronchiectasis and lymphoedema is consistent with yellow nail syndrome (YNS), but coexistent malignancy or other pathology should be excluded, particularly in view of the history of weight loss and asbestos exposure. Pleural fluid should be sent for cholesterol and triglycerides, cytology and culture, including mycobacterium TB. Thoracic CT and echocardiography should be performed. Overall, the most common causes for lymphocytic effusions are malignancy or TB. In a case series of 41 patients with YNS, around half had pleural effusions, which were predominantly lymphocyte-rich and more often bilateral than unilateral.[1] Chylothorax may also occur in YNS, classically appearing milky white due to high levels of triglycerides, but may be yellow or blood stained.

KB: No malignant cells were seen in the pleural fluid, and TB stain and culture were negative. Thoracic CT showed bilateral effusions, segmental consolidation in the left lower lobe and bilateral pleural plaques, but no pulmonary masses or lymphadenopathy. Echocardiography showed normal biventricular function and no evidence of a pericardial effusion. Previous medical records recorded a diagnosis of probable YNS following dermatology consultation, prior to the development of respiratory symptoms. The patient did not recall being informed of the diagnosis or other associated features of the condition. The pleural effusions rapidly reaccumulated, requiring repeat therapeutic aspiration within 1 month.

SCB: Interstitial and alveolar infiltrates are seen in patients with YNS. Considering the lack of an inflammatory response and the limited extent of the consolidation, it is unlikely that we are dealing with bilateral parapneumonic effusions. The CT scan does not show typical features of mesothelioma; however, pleura enhances late and in the early stages pleural malignancy may not be apparent. Thoracoscopy allows direct visualisation and biopsy of the pleura, while talc poudrage may provide therapeutic benefit. Pleural biopsy also offers a higher yield than pleural fluid for TB culture. Underlying immunodeficiency should be excluded.

KB: Sequential bilateral thoracoscopy and talc pleurodesis was performed under conscious sedation. Along with pleural tissue samples, 6.7 l of fluid was removed, with symptomatic benefit. Pleural fluid cholesterol, triglycerides and amylase were normal; repeat cytology was also negative. Tissue samples showed chronic fibrosing pleuritis and were negative for mycobacterial culture. Immunoglobulin levels were normal. Pleurodesis was unsuccessful, and the patient continued to require monthly thoracocentesis.

SCB: The clinical presentation and results of investigations, including histology, continue to support a diagnosis of YNS. Treatment options were discussed with the patient. Thoracocentesis was providing short-lasting benefits. Both this and the alternative option of inserting bilateral indwelling pleural catheters (to allow regular fluid drainage at home) may lead to lympho-depletion and increased risk of infection. Surgical pleurectomy may prevent recurrence, but thoracopic pleurodesis had been unsuccessful. Pleuroperitoneal and pleurovenous shunts have been used in this situation, but complications, including failure due to obstruction, are common. The patient was keen to explore less invasive options. A trial of a somatostatin analogue was proposed. There were at least two case reports showing a good clinical response to this treatment in patients with YNS, with both chylous[2] and non-chylous effusions.[3] This is a relatively safe treatment option; side effects include headache, bradycardia and gastrointestinal upset such as nausea, flatulence, diarrhoea and steatorrhoea. Cholelithiasis is associated with long-term use. The depot preparations are administered by deep subcutaneous injection and are viscous, requiring a wide bore needle.

The pathogenesis of the clinical features of YNS, including pleural effusions and lymphoedema, is not fully understood. Both impaired lymphatic drainage and increased capillary leakage due to

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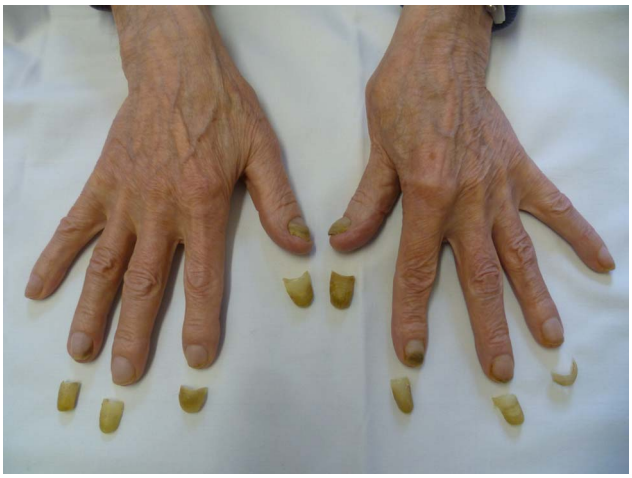

Figure 1 Demarcated lines with normal fingernail growth and yellow nails following several months of treatment.

microvasculopathy have been implicated. Somatostatin analogues reduce intestinal lipid absorption and lower the concentration of triglycerides in the thoracic duct. This could explain an improvement in chylous effusions related to leakage from the thoracic duct, but this is not the cause of the effusions, at least in most cases of YNS, nor would this fully explain the response seen in other features of the condition. Somatostatin receptors are expressed in lymphatic tissue and analogues have been shown to stimulate contraction of the lymphatic vessels and improve lymph flow. However, there may be other modes of action that are yet to be identified.

KB: Bilateral therapeutic aspirations were performed and a trial of octreotide was commenced, initially using the short-acting preparation. There was a marked improvement in the lymphoedema within a few days and he was switched to 4-weekly depot injections of Sandostatin LAR. After 4 weeks, there was only slight residual lymphoedema and normal fingernail growth was seen (figure 1). The patient's shortness of breath continued to improve over several weeks. At 6 months, small to moderate effusions were present on chest radiograph.

SCB: Spontaneous improvement in YNS may occur. After 18 months stability, the interval between injections was increased to 6 weeks. Unfortunately, this led to a substantial increase in the residual pleural effusions, with increasing breathlessness. Four-weekly treatment was resumed, and full symptom control was achieved within 3 months. Deterioration and subsequent clinical improvement following the changes in frequency of administration further support the efficacy of the treatment.

KB: The patient remained clinically stable for 3 years, requiring no further pleural aspirations, but his symptoms then returned. He developed increasing breathlessness, dry cough and lymphoedema. An increase in pleural effusion size was noted on chest X-ray. Therapeutic pleural aspiration was performed, and short-acting octreotide recommenced, but the effusions continued to worsen radiographically.

SCB: Given that the clinical response has muted, the patient may have developed tachyphylaxis to Sandostatin LAR. This phenomenon has been reported with octreotide use in other conditions, especially in chronic diseases such as acromegaly[4] and insulinoma,[5] although not, to our knowledge, in YNS. An alternative somatostatin analogue, such as lanreotide, may be of benefit.

KB: Repeat therapeutic aspiration was required prior to starting lanreotide. Although the appearance of new nail growth and control of lymphoedema occurred quickly, control of the breathlessness and pleural effusions was more gradual. However, within 6 months the patient's breathlessness had almost fully resolved. Therapeutic pleural aspiration was performed once over the intervening 18 months when he complained of a slight increase in breathlessness, with a marginal increase in the right-sided pleural collection. He remains stable on lanreotide.

SCB: On reflection, lipid restriction is another non-invasive option that we could have tried. There is some tentative evidence to suggest benefit in chylothorax, and it may also improve the chance of successful pleurodesis; however, I am unaware of any published evidence to support this in non-chylous effusions, such as seen in our patient. Various agents have been reported to improve the appearance of nails, including vitamin E. Interestingly, normal nail growth was noticed shortly after octreotide treatment began, except for one toenail. Nail clippings showed hyphae, and antifungal therapy was commenced (previous nail clippings had been negative). The lymphoedema noticeably improved within days of commencing treatment and pre-empted the improvement in respiratory symptoms, which occurred over weeks. This may be an early sign heralding a subsequent improvement in chest symptoms, but we would not interpret lack of an early response as treatment failure. The patient did not report an improvement in the clinical manifestations of his bronchiectasis; however, he had been stable in this regard for many years prior to starting treatment, with only infrequent exacerbations and low-volume sputum production. If the development of bronchiectasis in YNS is related to impaired drainage of tissue fluid from bronchial walls, somatostatin analogues may potentially be of benefit.

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