CASE BASED DISCUSSION

Dyspnoea, rhinorrhoea and pulmonary infiltrates in a healthy young woman

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Mark G Jones (MGJ): A 33-year-old woman was referred for a respiratory opinion. Three months prior she had developed a ‘bad cold’. This had persisted with intermittent rhinorrhoea, non-productive cough, pleuritic chest pain and a weight loss of 6 kg. Her symptoms had transiently improved following courses of co-amoxiclav and clarithromycin from her primary care physician and local district general hospital. The patient was previously healthy with no medical history of note. She had smoked minimally and drank little alcohol. There were no occupational or environmental exposures of note. Her family kept two cats and she had travelled to Spain 4 months prior to symptom onset.

On examination she appeared unwell. Bilateral submandibular and cervical lymphadenopathies were detected. Bilateral crackles were auscultated in the chest. Cardiovascular, gastrointestinal and neurological examinations were normal. The chest radiograph showed lingular consolidation and patchy right basal ground-glass opacities. Initial laboratory investigations identified a neutrophilia (25.2 \times 10^9/l) and a raised C reactive protein (CRP) (123 mg/l). Liver and renal function tests were within the normal range.

Katherine M A O’Reilly (KO’R): We have a previously healthy young woman who presents with pulmonary infiltrates, raised inflammatory markers, lymphadenopathy and weight loss. Although the initial presentation was suggestive of a community-acquired bacterial pneumonia (CAP), the response to broad-spectrum antibiotics is not as expected. So while CAP is unlikely, atypical infections including mycobacterial disease should be considered. The weight loss and lymphadenopathy are concerning and we should exclude an underlying malignancy such as lymphoma. In addition, HIV/AIDS, underlying inflammatory conditions such as vasculitis or cryptogenic organising pneumonia and recurrent aspiration should be considered.

MGJ: Further questioning identified no history of gastro-oesophageal reflux disease, swallowing difficulties or risk factors for aspiration pneumonia. Serologies including mycoplasma, coxiella, bartonella, toxoplasma, borrelia and histoplasma were negative. Lactate dehydrogenase level was 317 IU/l (normal range 0–525). Antibodies to the HIV were not detected. Immunological testing identified normal immunoglobulins, negative antinuclear antibody, negative rheumatoid factor, negative extractable nuclear antigen antibody panel and negative anti-neutrophil cytoplasmic antibody test.

A CT scan of the thorax showed widespread ground-glass opacity and centrilobular nodules with lingular consolidation and some early small airway dilatation (figure 1A). Pulmonary function tests (PFTs) were normal. Fiberoptic bronchoscopy identified normal endobronchial anatomy with purulent secretions in the lingula. These grew fully sensitive Haemophilus influenza. Mycobacterial culture, fungal culture and respiratory viral PCR panel were negative.

The opinion of an ENT specialist was obtained to investigate the rhinorrhoea and cervical lymphadenopathy. A cervical lymph node biopsy revealed only reactive changes and mycobacterial cultures were negative. Flexible nasendoscopy was normal, and the symptoms were felt to be consistent with intrinsic rhinitis. Mometasone nasal spray was commenced. A 2-week course of co-amoxiclav and azithromycin resulted in a clear symptomatic improvement and a decline in CRP to 12 mg/l.

KO’R: These investigations provide no evidence for atypical infection, vasculitis, immunodeficiency or malignancy. The clinical and radiological findings are mostly suggestive of a slow-to-resolve infection. As the patient has improved symptomatically and biochemically following further antibiotics, a period of close observation is warranted.

MGJ: Over subsequent weeks, the patient relapsed intermittently. Repeat CXRs identified waxing and waning pulmonary infiltrates. She was treated with antibiotics and in each case some improvement was noted, with deterioration following their discontinuation. The non-productive cough worsened and the patient developed breathlessness and rigours. Now systemically unwell, she required hospital admission. CRP was 154 mg/l. Multiple blood and sputum cultures were negative. Repeat CT scan identified extensive centrilobular nodularity in the basal lung segments, areas of focal consolidation within the left lower lobe and bronchial wall thickening. Following treatment with intravenous piperacillin/tazobactam, a clear clinical improvement was seen and CRP normalised. Repeat PFTs were abnormal with a mixed obstructive–restrictive pattern (forced expiratory volume in 1 second (FEV1) 1.62 L, 48% predicted; forced vital capacity (FVC) 2.43 L, 60%; FEV1/FVC 0.67; Transfer Factor (TLCO) 58%; Gas Transfer Coefficient (KCO) 81%). Combination inhaled corticosteroid/β2 agonist (budesonide/formoterol) was started.

KO’R: Clinically, this patient appears to have a relapsing or recurrent infection that is at least
partially responsive to anti-microbial therapy. The cause for this is currently unclear. Of most concern is the significant decline in the patient’s lung function. The radiological findings have also progressed and would suggest a differential diagnosis including bronchiolitis, extrinsic allergic alveolitis or possibly atypical fungal infection. A severe airway-based inflammatory process or form of bronchiolitis seems most likely. A partial response to antibiotics is noted with relapse following discontinuation. This is most suggestive of an infectious aetiology. In a previously healthy young woman, we must consider whether recurrent secondary infections are occurring due to an underlying disease process. Investigations, to date, have identified evidence of none of these: an atypical infection, a structural abnormality such as a pulmonary sequestration or bronchial carcinoid tumour, malignancy and vasculitis. We should consider the possibility of a functional immunodeficiency. If immunological testing is normal, then we should consider a surgical lung biopsy to further characterise the disease process.

MGJ: All further immunological testing was normal including lymphocyte phenotyping, functional antibodies and complement levels (C3/C4).

The patient agreed to proceed to a video-assisted thoracoscopic surgical lung biopsy (VATS). This identified a cellular bronchiolitis with patchy bronchiolitis obliterans (figure 1B). All cultures were negative.

KO’R: The biopsy findings are consistent with a form of bronchiolitis. In isolation, the finding of cellular bronchiolitis suggests a differential diagnosis including infectious or post-infectious bronchiolitis, subclinical aspiration, collagen-vascular disease-associated bronchiolitis, cryptogenic bronchiolitis, para-neoplastic pemphigus and diffuse panbronchiolitis. Integrated with the clinical and radiological findings, I felt a diagnosis of infectious or post-infectious bronchiolitis was most likely.

Given the concerning decline in PFTs, a trial of prednisolone (35 mg) and azithromycin (500 mg thrice weekly) was commenced. This resulted in a rapid improvement in the patient’s symptoms.

While attending a multidisciplinary conference on interstitial lung disease, I was struck by a talk given by KO’R describing the development of bronchiolitis in cases of recurrent aspiration. I discussed the case with him and he kindly agreed to review the pathology. His review corroborated the presence of an airway-centred mixed acute and chronic inflammatory process accompanied by microfoci of terminal bronchial organisation (oblitative bronchiolitis, figure 1B). No granulomas or infectious organisms were identified and no aspirated foreign material was seen. His differential diagnosis reflected that postulated on clinical grounds. Further characterisation of the patient’s respiratory disease was not possible histopathologically. The presence of bronchiolitis obliterans did underscore an ongoing reparative reaction, suggesting recurrent injury rather than the late sequelae of a single remote infection or inhalational insult. The patient’s symptoms and pulmonary function had improved significantly following treatment with prednisolone and a macrolide antibiotic. The history was again reviewed in detail. The patient denied any swallowing difficulties, excess alcohol use or use of sedating medications, seizure-like activity or any periods of reduced consciousness. However, the patient did describe intermittent rhinorrhea particularly at night time. Her husband now described intermittent episodes of coughing when supine. Given the persistence in symptoms, a further ENT opinion was obtained from a specialist in rhinology.

ENT: While clinically the rhinorrhea was consistent with intrinsic rhinitis no response to steroid nasal sprays had been observed. Given the intermittent but persistent rhinorrhea, episodic coughing and the pathological findings, suggesting recurrent injury we investigated for possible cerebrospinal fluid (CSF) leak. An MRI scan of the brain was suggestive but not diagnostic of an anterior skull-base defect. The patient, therefore, underwent endoscopic skull-base exploration. During anaesthetic induction, she was observed to aspirate a large volume of clear fluid from the nasopharynx. A defect in the cribriform plate was identified and closed.

MGJ: Progressive clinical improvement was seen. Corticosteroids were weaned and the CXR and PFTs had normalised. Later, after hearing the story and diagnosis, a friend who had accompanied the family on holiday in Spain recalled that the patient had been inadvertently ‘head-butted’ by her toddler in Spain. While the patient had not thought of the incidence during this illness, she did recall being ‘very dazed’.

KO’R: This patient had secondary subacute airway injury with inflammation and organisation as a consequence of recurrent
CSF aspiration. A fistula between the subarachnoid space and nasal sinuses, usually following frontal skull-base or nasoethmoid orbital fractures, causes CSF rhinorrhoea, which may be delayed by several months. A minority of cases are due to congenital abnormalities and tumours. A CT or MRI brain scan may localise large defects. Rhinorrhoea, containing β-2-transferrin, or a high glucose level is further diagnostic. Endoscopic repair is preferred when anterior CSF leak persists. Aspiration of CSF may induce pulmonary inflammation or infective pneumonia due to in-transit nasopharyngeal bacterial contamination. This patient recovered well post operatively and remains well with normal lung function.

Key learning points

▸ Aspiration can be a subtle clinical event that may go unnoticed by physician and patient alike.
▸ Every educational meeting provides the opportunity to interact with other professionals, to share expertise and to discuss and gain new perspectives on challenging cases.
▸ If a common clinical diagnosis is progressing atypically or recurring in addition to exploring alternative diagnoses, consider whether your diagnosis is correct but with an unusual or unsuspected aetiology.

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