CASE REPORT

A surprise behind a case of winter vomiting virus

Aikaterini Panopoulou, Erin Vermaak, Neil McHugh

Department of Rheumatology,
Royal National Hospital for
Rheumatic Diseases, NHS
Foundation Trust, Bath, UK

Correspondence to

Dr Aikaterini Panopoulou,
CathPanopoulou@gmail.com

SUMMARY

A 79-year-old man was admitted through the medical take with norovirus gastritis. Routine plain chest radiography demonstrated a right coin lesion. CT and subsequent positron emission tomography showed a right upper lobe mass consistent with primary bronchial carcinoma. The lesion was resected and histology revealed a granulomatous necrotising mass without evidence of dysplasia. Meticulous investigations for infectious and non-infectious causes of necrotising granulomatous diseases were repeatedly negative. His postoperative recovery was complicated by a hospital-acquired pneumonia and a pulmonary embolism. CT pulmonary angiography showed progression of the previously resected mass and repeat biopsy was similar to the initial. A clinical diagnosis of antineutrophil cytoplasmic antibody-negative vasculitis without extrapulmonary manifestations was made and immunosuppressive therapy was initiated with rapid clinical response.

BACKGROUND

When faced with a solitary pulmonary nodule, the clinician's priority is to exclude malignancy given its morbidity and potential curability if diagnosed and treated in time. As in our case, after the exclusion of a dysplastic process, and in the context of the presence of granulomatous tissue, other diagnoses must be considered.

CASE PRESENTATION

A 79-year-old man with a background of osteoarthritis and unilateral total knee replacement was admitted through the acute medical take with dizziness and vomiting. Vomitus samples were positive for norovirus and he was managed conservatively. However, a routine chest radiograph on admission demonstrated the incidental finding of a right upper lobe mass (figure 1). The patient was asymptomatic with no respiratory or constitutional complaints at the time. There was no history of asthma or connective tissue disease. He was a non-smoker and family history was unremarkable.

INVESTIGATIONS

He underwent a CT scan of the chest and abdomen, which showed a 3.2 cm right upper lobe mass and a solitary 14 mm right hilar lymph node (figure 2). Images were highly suspicious of a bronchial carcinoma and CT-guided percutaneous biopsy demonstrated fibrous tissue and elastin with extensive areas of amorphous necrosis.

As per the National Institute of Clinical Excellence (NICE) guidance on diagnosis and staging of lung cancer,¹ he had a PET scan which

showed a highly active right upper lobe spiculated mass, consistent with primary bronchial carcinoma. He underwent a right thoracotomy with upper lobectomy and chest wall resection.

Unexpectedly, histology revealed a granulomatous necrotising mass without evidence of dysplasia. This triggered a number of additional investigations to look for infective and other causes of his illness. Interferon- γ release assay for tuberculosis was repeatedly negative, as were fungal and mycobacterial cultures of blood and tissue specimens. *Aspergillus* antigen was absent and β -glucan, *Histoplasma* dimorphic serology, and tissue biopsy cultures for *Mycobacterium tuberculosis* (MTB) and *Nocardia* were negative. Streptococcal and *Legionella* urinary antigens were absent and urinalysis was repeatedly unremarkable. The 16S ribosomal RNA (rRNA) sequencing for bacterial fragments was negative. ACE levels were within normal limits and the autoimmune profile and antineutrophil cytoplasmic antibody (ANCA) was negative.

The patient's postoperative recovery was complicated by hospital-acquired pneumonia and pulmonary embolism. He then developed a persistent cough, elevated C reactive protein (CRP) and intermittent eosinophilia, which failed to settle despite appropriate antibiotic and anticoagulant treatment. CT pulmonary angiography showed progression of the previously resected mass and repeat biopsy demonstrated histological features similar to the initial biopsied specimen.

DIFFERENTIAL DIAGNOSIS

Granulomatous diseases commonly present with pulmonary involvement, and can be diagnostically challenging for clinicians, radiologists and pathologists. The commonest causes are infections, with MTB being the most frequently implicated in the developing world, and non-tuberculous mycobacteria being more common in the developed world, especially in immunocompromised patients. Other causative agents include fungi, such as *Histoplasma*, *Cryptococcus*, *Coccidioides* and *Blastomyces*, and other bacteria, including *Nocardia*, *Brucella* and *Burkholderia*. *Aspergillus* rarely causes granulomas, except in cases of chronic necrotising and allergic bronchopulmonary aspergillosis.²

In our case, a meticulous yet consistently negative search for infective causes, including negative testing for broad-range 16S rRNA—a highly sensitive and specific test for the identification of bacterial fragments—implied that infection was an unlikely cause of the patient's presentation.³ Sarcoidosis is the commonest cause of non-infectious granulomatous disease, and, as its clinical

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Figure 1 Chest X-ray.

course is often indolent, the key diagnostic process is excluding other, potentially more serious, causes. Other causes of non-infectious granulomatous diseases affecting the lung include berylliosis, hypersensitivity pneumonitis and vasculitis.²

Investigations including autoimmune serology, microbial testing and imaging studies may be helpful in the investigation of a solitary granulomatous pulmonary mass. However, in some cases, despite thorough and rigorous investigation, the diagnosis remains challenging. In our case, the diagnosis of ANCA-negative vasculitis presenting as a solitary pulmonary nodule was made on clinical and histopathological grounds.

Granulomatosis with polyangiitis (GPA, previously known as Wegener's granulomatosis) is known to cause nodular pulmonary disease, typically presenting with multiple bilateral nodules. Cases presenting with solitary nodules have been described, but only in the context of ANCA positivity.⁴ To the best of our knowledge, this is the first documented case of GPA in an adult patient presenting as a solitary pulmonary nodule.

TREATMENT

After diagnosis, immunosuppressive therapy with oral steroids was initiated resulting in a rapid clinical and biochemical response, with resolution of cough and normalisation of CRP and eosinophil count (figure 3).

OUTCOME AND FOLLOW-UP

Serial chest radiographs showed no evidence of progression. Azathioprine was started as maintenance therapy and the patient has remained well at 1, 3, 6 and 12 months of follow-up.

DISCUSSION

Given the atypical nature of the presentation and ongoing concerns over the potential underlying infection or malignancy, induction therapy began with steroids alone. The authors, however, note that induction therapy for GPA would typically include steroids in combination with either cyclophosphamide or methotrexate.⁵ In this case, remission was achieved quickly with steroid monotherapy, and azathioprine was then started as a maintenance agent. Evidence-based guidelines recommend azathioprine or methotrexate as maintenance agents. Other treatment modalities, such as biologics (eg, rituximab) and plasma exchange, may be indicated in certain circumstances.⁵

While almost all of the systemic vasculitides can involve the lung, it is the small-vessel or ANCA-associated vasculitides

Figure 2 CT of the chest.

(AAVs), including GPA, microscopic polyangiitis (MPA), eosinophilic GPA (eGPA, previously known as Churg-Strauss syndrome), and idiopathic pauci-immune pulmonary capillaritis that are responsible for the vast majority of cases. These small-vessel vasculitides involving the pulmonary vasculature are grouped together as they share common clinical features and pathologies, and are frequently, but not universally, associated with ANCA positivity.⁶

The radiological presentation of small-vessel vasculitides involving the lower respiratory tract is diverse. Lung involvement can manifest as nodular disease, most commonly presenting with multiple, bilateral nodules, with smooth rather than irregular margins, involving subpleural regions. Other pulmonary manifestations include lung masses, airspace opacification, ground-glass appearances and bronchial thickening. Disease limited to the lung usually presents with multiple nodular lesions with or without cavitation.⁷ A review of the published literature revealed case reports of histopathologically confirmed ANCA-negative vasculitides confined to the pulmonary vasculature presenting with solitary giant bulla⁸ and multiple pulmonary nodules with cavitation.^{9–10} One case of cytoplasmic ANCA (c-ANCA)-negative GPA presenting with a solitary pulmonary nodule has been reported in a paediatric patient with weakly positive perinuclear ANCA (p-ANCA).¹¹

In contrast to the implications of the term 'ANCA-associated vasculitides', the presence of a positive ANCA is not a *sine qua non* for the diagnosis of these conditions. The European Vasculitis Study Group (EUVAS) suggests the following criteria to make a diagnosis of AAVs: (1) history of a chronic inflammatory disease lasting at least 4 weeks, with (2) exclusion of other causes such as infection or malignancy, supported by (3) characteristic histology on biopsy, and/or (4) a positive ELISA for either proteinase 3 (PR3) or myeloperoxidase (MPO) antibodies and a classical c-ANCA on immunofluorescence.¹² The 2012 Chapel Hill Consensus Conference definition of AAVs is a necrotising vasculitis, with few or no immune deposits, predominantly affecting small vessels (ie, capillaries, venules, arterioles or small arteries), and associated with MPO-ANCA or PR3-ANCA.¹³ However, it is recognised that not all patients with AAVs will have a positive ANCA, and has been suggested

Figure 3 Eosinophil fluctuations.

that patients with so-called ANCA-negative AAVs may have an ANCA that cannot be detected with current methods, an ANCA of as-yet-undiscovered specificity, or pathogenic mechanisms that do not involve ANCA at all.¹²

The ANCA subtypes, c-ANCA (cytoplasmic staining pattern, typically with PR3 specificity) and p-ANCA (perinuclear staining pattern, typically with MPO specificity) have a high diagnostic yield for AAVs in the right clinical context.¹⁴ More specifically, c-ANCA has high sensitivity (90–95%) and specificity (90%) in active systemic GPA. In comparison, p-ANCA lacks sensitivity and may be more helpful in suggesting, rather than confirming, a diagnosis of vasculitis. For both investigations, the positive predictive value is significantly increased when applied to a high-risk patient as judged on clinical grounds, and, in the right clinical context, a positive ANCA may make a tissue diagnosis non-essential.⁶ It is suggested that ANCA should be tested by both indirect immunofluorescence and ELISA in order to maximise the sensitivity and specificity of the diagnostic test.¹⁵

Approximately 90% of patients with active, generalised GPA are ANCA positive. Therefore, up to 10% of patients with this form of GPA may be ANCA negative, although in more limited forms of the disease, such as cases predominantly involving the upper airway tract or with renal sparing, ANCA may be positive in only 50–60% of cases.^{12 14 15} The strong association of ANCA with AAVs has led to the assumption that they are associated with the pathogenesis of these diseases. Recent studies support, but do not prove, the aetiopathogenic role of ANCAs in AAVs.¹⁴ Apart from the involvement of ANCA, these studies also support the role of cellular and humoral autoimmune mechanisms, in particular the migration of T effector memory cells to target organs in active disease, and impaired functioning of regulatory T cells. The role of adaptive immunity after exposure to microbes, especially *Staphylococcus aureus*, in triggering disease is also under investigation.¹⁴

The clinical utility of ANCA as a marker of disease activity in established vasculitis is not entirely clear. ANCA titres are generally high at presentation and fall with immunosuppression and disease control. Persistent or re-emerging ANCA in the first-year post diagnosis is associated with relapse in both GPA and MPA, whereas those patients with persistently negative ANCA during follow-up have a lower incidence of relapse.¹⁵ Clearly, treatment of these conditions should be directed by clinicopathological parameters, however changes in ANCA titre may predict relapse or indicate other concurrent pathologies, such as infection, and

should be used critically in the assessment and management of these patients.¹⁵

Learning points

- ▶ The diagnosis underlying a solitary lung nodule can be challenging and non-malignant causes should be considered, especially in non-smokers.
- ▶ Lung involvement in antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAVs) is common and has various patterns, including solitary lesions.
- ▶ ANCA is strongly associated with but not a sine qua non for the diagnosis of AAVs.
- ▶ Although there is good evidence that ANCA is involved in the pathogenesis of AAVs, other factors need to explain ANCA-negative cases.

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Competing interests None.

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