Post-mortem findings in a case of fatal vasculitis

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Abstract

The term “vasculitis” refers to a family of conditions characterized by inflammation of blood vessels. These processes can affect small, medium or large vessels, and have a wide range of clinical presentations, histological appearances, and prognoses. As histopathologists, we usually see these vasculitides in a partially or well-treated state; patients have often commenced local or systemic therapy by the time of their biopsy, and this can significantly affect the histological appearances. This case report describes the clinical history and associations of a fatal case of granulomatosis with polyangiitis (GPA), formerly known as Wegener’s granulomatosis. GPA is an uncommon multisystem vasculitis, classically involving the respiratory tract and kidneys, though other systems are also known to be affected including the GI tract, skin, and joints among many others. The post-mortem examination identified the immediate cause of death, and demonstrated very well the typical histological features that may be observed in this condition.

Keywords Alpha-1 antitrypsin deficiency; granulomatosis with polyangiitis; vasculitis

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Case report

A man in his late fifties was admitted to hospital following a fall at home. He had been complaining of ‘circulation problems’ in his hands and feet for several weeks, and had been trying various home remedies for this, but had not yet sought medical attention. His past medical history included alpha-1-antitrypsin deficiency (PiMZ genotype), chronic obstructive pulmonary disease (COPD), gastro-oesophageal reflux disease, and hypertension. His medications included atorvastatin, esomeprazole, lisinopril, and inhalers.

On arrival at hospital, examination showed a purple rash over his arms and legs, which was reportedly worsening over the past week, and necrotic changes to the tips of his digits. He also had a productive cough. He was apyrexial, heart rate 119/minute, blood pressure 112/69 mmHg, and though his femoral pulses were palpable, his popliteal and foot pulses could not be identified. A chest X-ray showed multiple ill-defined lung nodules, and a CT head was unremarkable. The initial differential of the treating team was appropriately broad, including vasculitis, sepsis with possible septic emboli, or a paraneoplastic phenomenon such as cryoglobulinaemia. After taking blood cultures, he was rapidly commenced on broad spectrum antibiotics, and a vasculitis screen was sent.

Despite being initially stable, the patient suddenly collapsed less than one day into admission, and was found to be in cardiac arrest. He remained in ventricular fibrillation and pulseless electrical activity throughout a prolonged resuscitation effort, which was ceased after over 1 hour. The case was referred to the Coroner as no cause of death could be provided by the clinical team.

Following his death, the initial serological investigations came back as showing raised serum IgA, ANCA-PR3 (c-ANCA), and anti-Scl-70 antibody. Blood cultures showed no growth.

At post-mortem examination, the previously described rash was seen to involve the extensor surfaces of all limbs, and small red/purple puncta were noted in and around the nostrils. Features of medical intervention/cardiopulmonary resuscitation were present, including venepuncture sites and bilateral rib fractures. The pericardium showed scattered red puncta over the exterior, and a 5 mm pale nodule was noted on the posterior epicardial surface. The coronary arteries showed moderate background atheroma only. The lungs were heavy, both weighing 1000—1100 g and showed multiple nodules measuring up to 60 mm in diameter, with a yellow speckled cut surface. The kidneys had a granular and mottled outer surface, and the liver had a nutmeg appearance. The remaining organ macroscopic appearances were within normal limits. Blocks were taken from the epicardial nodule, lung nodules and skin rash, in addition to routine histological sampling of all major organs.

Histology of the epicardial nodule showed it to be a large, densely inflamed coronary artery branch with a thrombus within the lumen (Figure 1a). The myocardium showed areas of contraction band necrosis and infiltrates of chronic inflammatory cells (Figure 1b). Sections from the lungs showed the nodules to be large areas of confluent necrosis, with prominent vascular inflammation (Figure 1c). Numerous foci of granulomatous inflammation of the vessel walls were identified, with multinucleate giant cells present in the tunica media (Figure 1d). The kidneys showed a range of histological appearances, including perivascular and interstitial inflammation, and well as glomerular inflammation with cellular crescents (Figure 1e); background globally sclerosed glomeruli were also seen. Sections of the skin were taken from the interface of the rash and surrounding normal tissue, and these showed areas of necrosis of the dermis and epidermis, with prominent mixed inflammation in the vicinity of vessels in the dermis (Figure 1f) and

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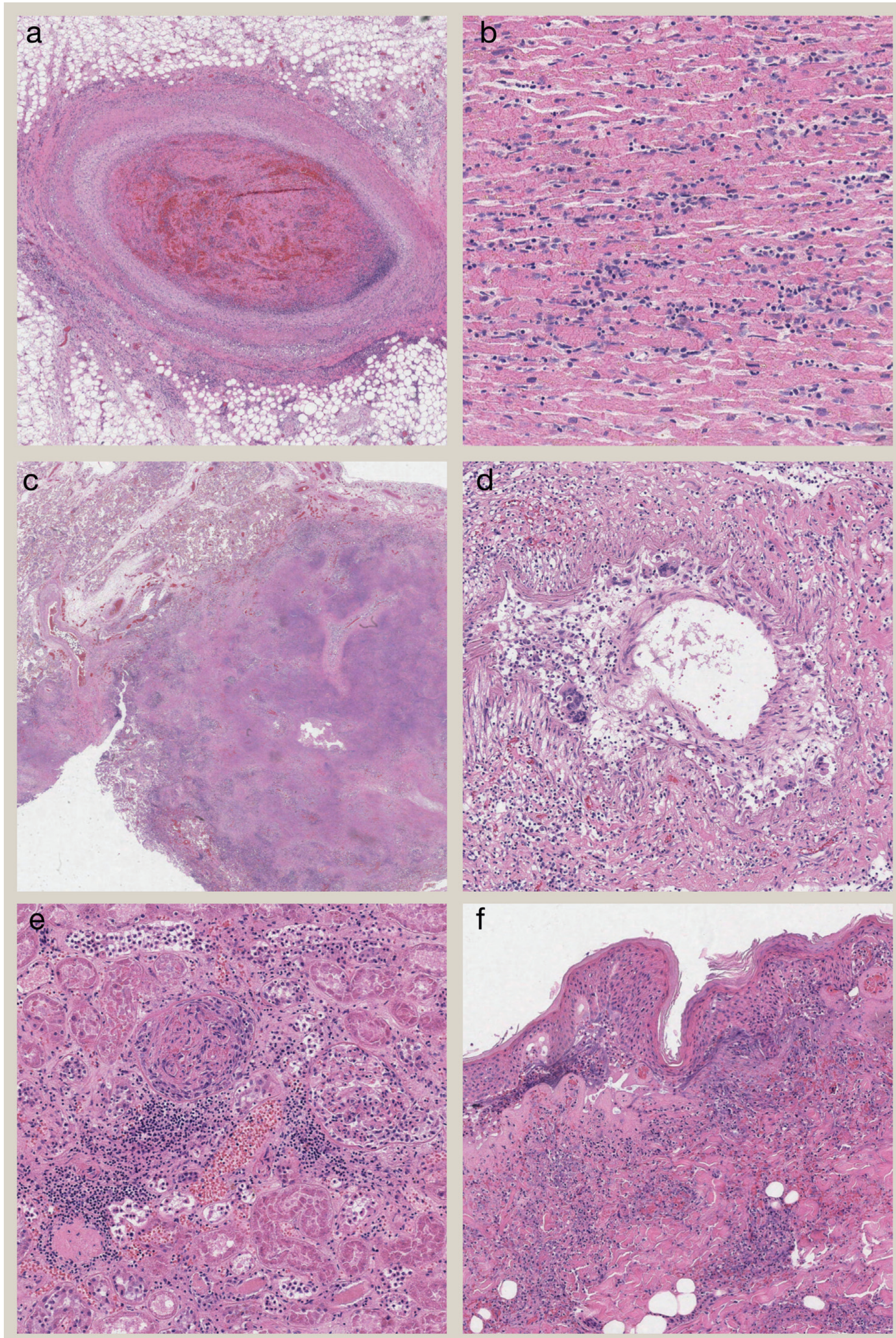

Figure 1 Histology of a fatal case of granulomatosis with polyangiitis (GPA). (**a**) Low power view of a thrombus within a severely inflamed coronary artery branch. This corresponded to the epicardial nodule observed macroscopically and was considered to be an essential part of 1a in the cause of death formulation. Inflammation can be seen throughout the wall of the vessel. (**b**) High power view of the left ventricular myocardium, showing infiltrates of chronic inflammatory cells and contraction bands. This myocarditis also factored into part 1a of the cause of death formulation. (**c**) Low power view of the edge of a lung nodule, demonstrating the interface between normal post-mortem lung on the left, and confluent necrosis on the right. Such nodules were seen in all lobes bilaterally. (**d**) High power view of a vessel in the lung, near the interface of the normal and necrotic tissue. Numerous multinucleated giant cells can be seen within the vessel wall, on a background of marked chronic inflammation, histologically consistent with GPA. (**e**) High power view of the kidney, showing marked chronic inflammation of the interstitium and glomeruli, with apparent cellular crescent formation. (**f**) High power view of the skin, at the interface between normal and necrotic tissue at the edge of the rash. There is marked mixed inflammation, with necrosis and early separation at the dermoepidermal junction.

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subcutis. The liver histology showed congestion, though no convincing PAS positive granules were seen. The remaining histology was unremarkable.

Integrating the above findings, the cause of death felt to be most in keeping with the patient's acute collapse was given as:

1a Coronary artery thrombosis and myocarditis
1b Granulomatosis with polyangiitis
1c —
2 —

Discussion

Several different criteria have been proposed for the diagnosis of GPA, though a frequent histological criterion is the presence of granuloma/giant cells in the walls of medium sized vessels.[1] The vessels in the lung nodules in this case demonstrated this feature very well. This patient was also known to be positive for ANCA-PR3 (c-ANCA), the typical pattern for GPA.

Interestingly, this gentleman had a documented history of alpha-1-antitrypsin deficiency (A1ATD) with a PiMZ genotype. A1ATD is known to be associated with the development of GPA,[2] and PiZ heterozygosity is suggested to be a possible poor prognostic indicator in the context of GPA.[3] A more recent study has suggested that homozygotes for the Z or S alleles, and compound SZ heterozygotes, may be at even higher risk of developing GPA than heterozygotes with an M allele.[4] Other systemic vasculitides have been reported in association with A1ATD, including microscopic polyangiitis and Henoch-Schönlein purpura (HSP).[5]

In conclusion this case shows clear examples of the histology of GPA, and demonstrates its association with A1ATD. These learning points are useful not only in the post-mortem context, but also when reviewing surgical specimens from patients with known A1ATD or suspected vasculitis. ◆

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Practice points

- Several vasculitides, including granulomatosis with polyangiitis, have an established association with alpha-1-antitrypsin deficiency
- Classical histological features of GPA include granulomatous/giant cell inflammation of the walls of small-medium sized vessels, and glomerular crescents
- Acute thrombosis within inflamed vessels is a potential cause of death in vasculitis cases
- Defining features of GPA, such as giant cell inflammation, may be patchy — thorough sampling of lesions in all affected systems is advised, in addition to routine post-mortem blocks
- GPA can progress rapidly over a course of weeks, and patients may present at advanced stages in such cases

Single best answer questions

1. What microscopic pattern of vasculitis is most commonly observed in patients with GPA?

A Aortic inflammation
B Giant cell inflammation in small-medium sized vessels
C Granulomatous inflammation in large vessels
D Non-necrotizing granulomatous inflammation
E Renal artery involvement

Answer: **B**

2. What is the association between vasculitis and A1ATD?

A GPA, but not HSP, is associated with A1ATD.
B Microscopic polyangiitis, but not GPA, is associated with A1ATD
C A1ATD is associated with several vasculitides, including GPA, HSP and microscopic polyangiitis
D A1ATD has no association with vasculitis
E Over 50% of systemic vasculitides are associated with A1ATD.

Answer: **C**

3. Which A1ATD genotype(s) is/are most commonly seen in association with vasculitis?

A The Z allele, but not the S allele, is associated with vasculitis
B The S allele, but not the Z allele, is associated with vasculitis
C The S and Z alleles are both associated with vasculitis, including in cases of SZ heterozygosity
D The S and Z alleles are both associated with vasculitis, but SZ heterozygosity is protective against vasculitis
E The M allele is most strongly associated with vasculitis

Answer: **C**

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