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Novel Cause of Sudden Cardiac Death IgG4-Related Disease

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A 61-year-old black woman with hypertension, dyslipidemia, sickle cell trait, and α -thalassemia presented with a 3-week history of progressively altered mental status and seizures. Laboratory studies demonstrated multiple autoantibodies, including antinuclear antibody (speckled, titer 1:640) and anti-Smith and anti-ribonucleoprotein (both positive by enzyme immunoassay). Of note, her erythrocyte sedimentation rate was elevated at 86 mm/h (reference range 4–30 mm/h), her C-reactive protein was elevated at 4.2 mg/dL (0.0–0.5 mg/dL), and her serum IgG level was normal at 1510 mg/dL (751–1560 mg/dL). ECGs early in her hospitalization demonstrated normal sinus rhythm. Initial imaging studies including chest radiograph, echocardiogram, and thoracic computed tomography showed normal aortic root caliber with minimal arteriosclerosis and mild cardiomegaly. Two weeks after admission, follow-up imaging revealed slight dilation of the ascending aorta to 4 cm on chest computed tomography (Figure 1A) and minimal tortuosity of the descending aorta on chest radiograph, which was not explored further.

After a long intensive care unit stay and extensive clinical evaluation that included brain biopsy, a presumptive diagnosis of lupus cerebritis was made. Treatment with pulsed high-dose methylprednisolone followed by 2 cycles of intravenous cyclophosphamide led to a remarkable improvement. Clinically, the patient recovered from profound neuropsychiatric debilitation to a normal, independently functioning status. She was maintained on outpatient prednisone and mycophenolate mofetil with normalization of erythrocyte sedimentation rate, although 1 year later the erythrocyte sedimentation rate rose again to 77 mm/h. Imaging 1 year after hospital discharge was notable only for two 1-mm aneurysms of the left internal carotid artery with a normal aortic arch (Figure 1B). After 15 months of successful treatment, in the midst of a slow prednisone taper, she unexpectedly was found dead in bed at home.

Postmortem examination was notable for a 3-cm dissection of the ascending aorta that had propagated in a retrograde fashion along the proximal 1.5 cm of the left main coronary artery. This coronary dissection compressed the arterial lumen, causing the patient's sudden cardiac death (Figure 2A). Microscopic examination of the proximal aorta revealed

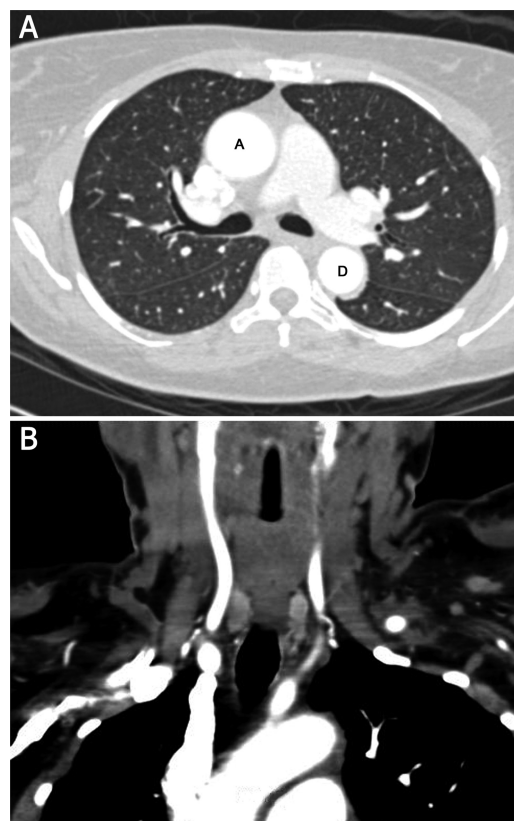


Figure 1. A, Computed tomography of the chest with intravenous contrast 2 weeks after admission, demonstrating a slight (4 cm) dilation of the ascending aorta that was not noted previously. A indicates ascending aorta; D, descending aorta. B, Computed tomography angiogram 3 months before death, demonstrating normal configuration of the aortic arch and bilateral carotid arteries, without evidence of aneurysm or stenosis.

a marked lymphoplasmacytic arteritis without giant cells, primarily in the media, where the dissection occurred, but also involving the intima and adventitia (Figure 2B). A vascular survey identified a plasma cell-rich infiltrate that affected the entire aorta (thoracic and abdominal), as well as the bilateral common iliac arteries, left renal artery, and bilateral internal carotid arteries (Figure 2C). The coronary

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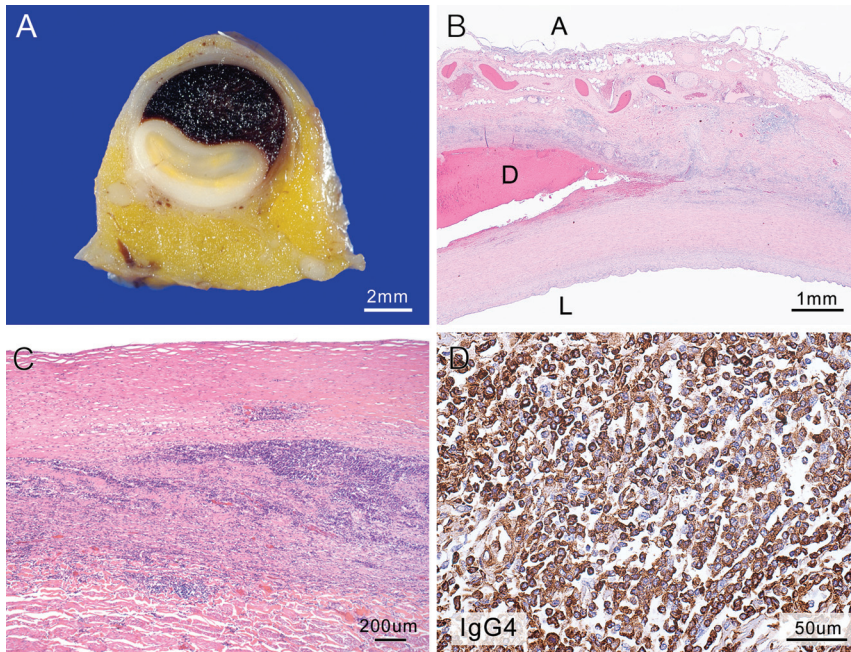


Figure 2. Gross and histological autopsy findings of IgG4-related arteritis causing sudden cardiac death. **A**, Left main coronary artery dissection. **B**, Histological section of the leading edge of the proximal aortic dissection, demonstrating lymphoplasmacytic inflammation present in the media of the vessel (hematoxylin and eosin; original magnification $\times 1$). L indicates lumen; D, dissection; and A, adventitia. **C**, Histological cross section of the left common iliac artery with lymphoplasmacytic inflammation, most prominent in the media (hematoxylin and eosin; original magnification $\times 20$). **D**, Immunohistochemical stain of the aorta for IgG4 with cytoplasmic positivity in $\approx 80\%$ of plasma cells (original magnification $\times 160$).

arteries, right renal artery, and splenic artery were unaffected. An immunohistochemical stain demonstrated cytoplasmic IgG4 staining within the plasma cells (Figure 2D), with an IgG4:IgG ratio of $\approx 80\%$.

Discussion

IgG4-related systemic disease (IgG4-SD) is a rare cause of nonnecrotizing ascending aortitis, occurring in 0.5% to 1.6% of thoracic aorta and $\approx 5\%$ of abdominal aorta resection specimens.^{1,2} IgG4-SD has been described in a variety of locations, including the pancreas, biliary tree, salivary gland, lung, kidney, and retroperitoneal soft tissue.^{1,3} The process is insidious, is typically seen in older males, and often sequentially affects 1 organ at a time.¹ Serum IgG4 levels are frequently but not universally elevated,¹ and increased antinuclear antibody, C-reactive protein, and erythrocyte sedimentation rate have been reported.² Most patients experience rapid symptomatic improvement and decreasing levels of serum IgG4 with glucocorticoid therapy.⁴

In this case, the admitting neurological episode was presumptively diagnosed as lupus cerebritis with no specific findings on brain biopsy and a normal total serum IgG level. Neither imaging at the initial presentation nor 1 year later identified vascular abnormalities that would indicate a concern for IgG4-SD, although the slight aortic dilation may have potentially indicated developing aortic disease. The postmortem findings raise the possibility that the earlier neurological symptoms were a manifestation of IgG4-SD,

which partially responded to the correct therapy despite the uncertain diagnosis.

The pathogenesis of IgG4-related disease remains poorly understood, although the leading theories point to an autoimmune or allergic mechanism.² Current hypotheses include abnormal regulatory T cells that drive plasma cell differentiation or an unknown antigen that elicits a robust Th2 immune response.³ In addition to chronic organ damage caused by inflammation and fibrosis, the life-threatening potential of acute complications of IgG4-SD is now apparent. We demonstrate that in patients with unusual clinical manifestations suggestive of autoimmune disease, a suspicion for IgG4-SD may facilitate diagnosis and intervention. This case is notable as the first report of sudden death caused by vascular IgG4-SD with one of the most extensive distributions of IgG4 arteritis yet described.

Disclosures

Dr Pasternack is Chief Executive Officer of Asklepios Pharmaceuticals, LLC. The other authors report no conflicts.

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