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Research letter

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Intimal Granulomatous Angiitis in Sarcoid Pulmonary Vasculitis: Worth Remembering

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To the Editor,

Sarcoidosis is a systemic disease characterized by non-necrotic epithelioid granulomas that preferentially involve the respiratory tract (1). In pulmonary sarcoidosis, granulomas develop throughout the lung parenchyma, notably in the perivascular and peribronchiolar interstitial spaces, as well as in the walls of small pulmonary arteries and veins (2). This vascular involvement defines sarcoid vasculitis, which was classified among the vasculitides associated with systemic diseases at the 2012 Chapel Hill consensus conference (3). Pulmonary hypertension (PH) is a major complication that occurs in 5% of patients with sarcoidosis and may cause death or require lung transplantation (4,5,6). Sarcoid granulomatosis of the pulmonary vessels was documented in 9% of 128 open lung biopsies and 100% of 40 autopsies reviewed by Rosen *et al.* and Takemura *et al.* respectively (7,8). Broad agreement exists that granulomas first develop within the perivascular interstitial sheaths adjacent to the lymphatics and subsequently compress or invade the blood vessels from the outside in. However, work reported in the 1970s by Carrington and by Rosen *et al.* demonstrated intimal or transmural granulomas that were not continuous with the perivascular parenchymal granulomas (2,7). This finding suggests angiitis mechanisms in addition to, or instead of, the spread of adjacent parenchymal granulomas.

We recently identified a pattern of granulomatous intimal and transmural angiitis when reviewing lung explants from a 54-year-old Caucasian former smoker who had received a double-lung transplant for very severe COPD and emphysema (FEV1 less than 25% of

predicted). Mild asymptomatic pulmonary sarcoidosis had been diagnosed 2 years before the procedure when a pre-transplantation assessment showed non-compressive bilateral hilar and mediastinal lymphadenopathy on chest CT, with enhanced 18F-FDG uptake and typical non-necrotizing granulomas by endobronchial ultrasound (1). No sarcoid involvement outside the lungs was identified. At transplantation in 2016, the mean pulmonary artery pressure was 34 mmHg at right heart catheterization and the capillary pressure was normal.

Pathological findings were similar in all explant samples across the recipient lung lobes. Severe diffuse emphysema consistent with the reason for transplantation was seen (not shown) in conjunction with typical full-blown pulmonary sarcoidosis manifesting as numerous florid intranodal (1A), parenchymal, and pleural granulomas (1B). Both compression of the pulmonary vessels by adjacent peripheral granulomas (1C) and vascular transmural granuloma spread (1D) were visualised (Figure 1). More surprisingly, numerous independent intimal granulomas bulging into the vessel lumina were observed (1E-J), chiefly within the walls of intra-acinar vessels and septal pulmonary veins. Granulomas composed of CD68+ macrophages and macrophage-derived epithelioid cells (1G, H) associated with lymphocytes were clearly organized in the intimal space and overlaid by endothelial cells, without luminal thrombosis. Macrophages extended from these granulomas through the vascular wall (1F, H). Primitive unorganized granulomas containing giant cells (1J) were also observed, as well as circumferential intimal infiltration by CD68+ macrophages (1L) at a distance from the granulomas.

This finding of intimal granulomas should routinely prompt consideration of other forms of granulomatous angiitis such as polyarteritis nodosa or granulomatosis with polyangiitis. These diagnoses were ruled out in our patient by the medical history, abundant typical florid granulomas within the mediastinal lymph nodes and lung parenchyma in all sampled lobes, and absence of fibrinoid necrosis within vessel walls.

Four episodes of cellular rejection occurred within 1 year after transplantation. Sequential transbronchial lung biopsies indicated two sarcoidosis relapses with intra-parenchymatous granulomas, 1 (2017) and 5 (2021) years after transplantation, during prednisone 10 mg/d and tacrolimus therapy, respectively, prompting a switch from tacrolimus to everolimus.

The findings in our patient are reminiscent of previous reports of intimal or mural granulomatous arteritis and phlebitis (2,7,8). The granulomas confined to the vessel walls at a distance from peripheral granulomas and the subendothelial intimal granulomas strongly support a non-classical pattern of vasculitis coexisting with, and independent from, the classical spread of perivascular granulomas through the vessel wall, in keeping with the suggestion nearly fifty years ago by Rosen *et al*. (7). Moreover, as illustrated in Figure 1J, marked intimal infiltration by macrophages and monocytes, often combined with lymphocytes, was observed at a distance from the granulomas, with cells seen to cross the endothelial layer. This infiltration, together with the formation of unorganized intimal granulomas, might be a first step in the development of vasculitis pathology. Moreover, injury to small lung vessels at a distance from, or in the absence of, granulomas has been documented in patients with sarcoidosis, including at the ultrastructural level (9). Inflammatory vasculitis distinct from, but synchronous with, granulomas has been described within sarcoid skin lesions (10). These data support the hypothesis of inflammatory luminal vasculitis as an alternative pattern of sarcoid angiitis, at least at some point in the course of the disease.

Why this pattern is no longer described in recent work on vascular involvement in pulmonary sarcoidosis deserves discussion. Conceivably, it may be transient, being present only at the initial or florid phase of sarcoidosis. Our patient had recent-onset sarcoidosis with widespread, florid, nonfibrotic granulomas, and the transplantation may have allowed

detection of the early steps of sarcoid vasculitis. In keeping with this possibility, between 1976 and 1992 when descriptions of this pattern were published, surgical lung biopsies were widely performed for the diagnosis of interstitial lung diseases including sarcoidosis (2,7,8).

The role for cellular and humoral immunity in PH, including the idiopathic form, is a focus of growing attention (11). The part played by monocytes and macrophages is of special interest. The vascular inflammation chiefly mediated by macrophages and lymphocytes in this non-classical pattern of sarcoid vasculitis may be pivotal in the development of PH in sarcoidosis and may explain, at least in part, some of the pathological features such as septal fibrosis responsible for vein occlusion even in the absence of local fresh granulomas or granuloma ghosts.

The spread of intimal subendothelial granulomas in contact with endothelial cells suggests an immune conflict at the blood-vessel interface. In the late 1970s, several studies identified circulating immune complexes in patients with sarcoidosis, notably at the florid phase (12,13). The possible involvement in sarcoidosis of autoimmunity with autoantibody production is being actively investigated (14). Although pulmonary sarcoidosis may be chiefly related to airborne triggers or antigens, bloodborne humoral or cellular autoimmune factors targeting structural lung components may be involved also, as suggested by the rapid recurrence of this systemic disease in our patient.

In conclusion, the replication of older findings in our patient may suggest new avenues of research into the various PH patterns associated with sarcoidosis and, more specifically, may point to hypotheses for explaining the presence of PH despite limited pulmonary involvement (4,15).

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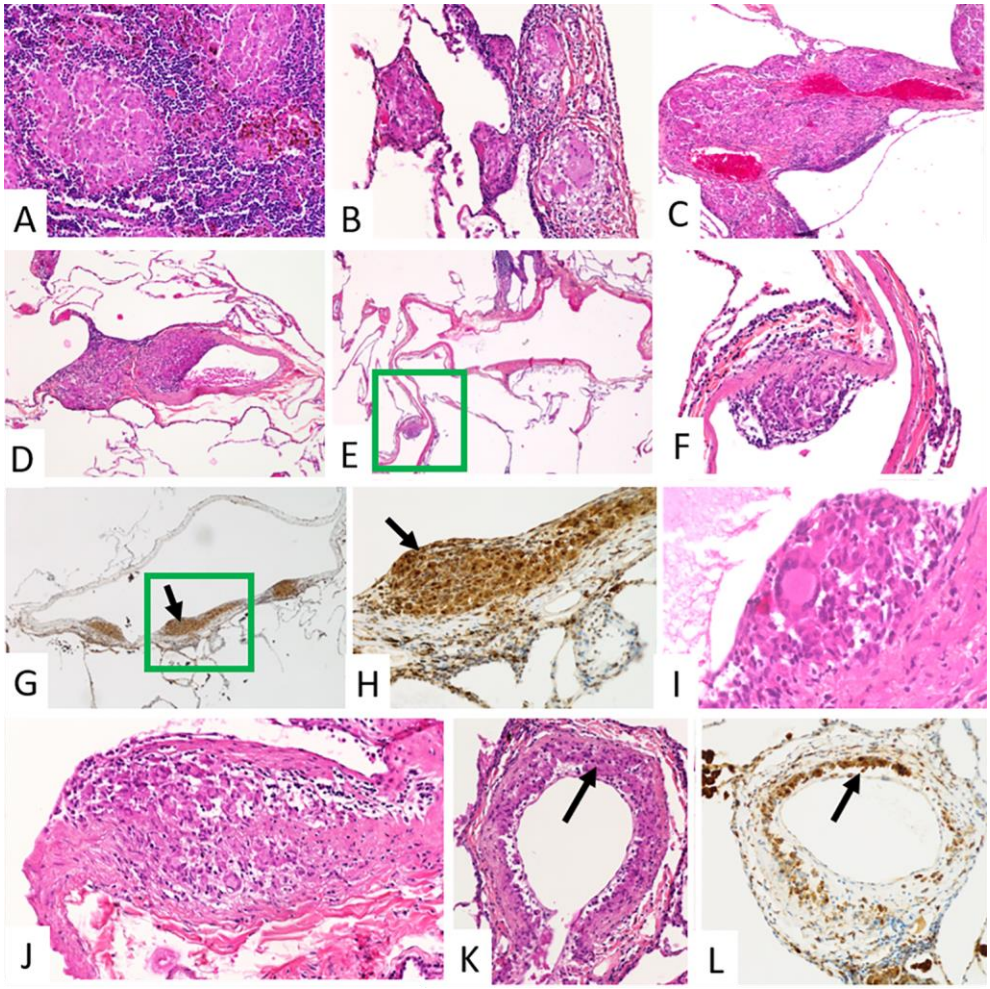
Figure legend

Light microscopy of mediastinal lymph node (A) and lung (B-L) explant samples (hematoxylin-eosin staining except CD68 immunohistochemistry for G, H, and L).
A: florid nodal granulomas (x250). **B:** pleural granulomas (x100). **C, D**: vascular compression by granulomas with (D) transmural extension (x50). **E, F**: intimal granuloma in a pulmonary vein wall; F is a magnification of the box in E (E: x50; F: x125). **G, H**: intimal granuloma in a pulmonary vein wall after CD68 immunolabelling showing contact with the endothelial layer (arrow); H is a magnification of the box in G (G: x50; H: x125). **I, J:** higher magnification of intimal (I) and transmural granulomas (J) in an arterial wall (I:x500, J:x 300). **K, L**: intimal infiltration by macrophages (arrow) in a small pulmonary artery wall, highlighted by CD68 immunolabelling (L) (x125).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