Necrotizing sarcoid granulomatosis with extrapulmonary involvement

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Necrotizing sarcoid granulomatosis was first described by Liebow [1] in 1973. He defined five forms of pulmonary angiitis and granulomatosis unrelated to infection or connective tissue disorders: Wegener’s granulomatosis; limited Wegener’s disease; lymphomatoid granulomatosis; bronchocentric granulomatosis; and NSG. Isolated reports of patients with this disorder have appeared in the literature [2–5], describing pulmonary lesions with sarcoid-like granulomas showing varying degrees of noncaseous necrosis and granulomatous arteritis [1, 3, 4, 6, 7]. Extrapulmonary involvement is rare [3, 6–8], and the histological features of NSG outside the lungs have been reported only once previously [6].

We report the case of a woman who developed granulomatous lesions in the left orbit and the right lung 12 yrs apart. Both lesions showed the histological hallmarks of NSG.

Case report

The patient, who was born in 1944, was a mother and housewife, and had smoked 10–20 cigarettes a day all her life. She presented on several occasions between 1974 and 1976 at the Aberdeen Royal Infirmary with headaches, which were treated as migraine or tension headaches with limited success.

In March 1979, she was admitted with fever, global weakness of the right upper limb and an extensor plantar response. Computerized tomography (CT) head scan and lumbar puncture revealed no abnormalities. Erythrocyte sedimentation rate (ESR) was normal, and antinuclear factor (ANF) and rheumatoid factor (RF) were negative. The illness improved spontaneously over several days.

In December 1981, the patient was readmitted with fever, headache, photophobia and diplopia. Neurological examination revealed a left 6th nerve palsy, a left lower motor neurone 7th nerve palsy, and reappearance of the right extensor plantar response. Her ESR, ANF, RF, and CT head scan were unremarkable, but the cerebrospinal fluid (CSF) protein was raised at 900 mg·L−1 (reference <430 mg·L−1), with normal glucose and no pleocytosis. Oligoclonal bands were absent. A vasculitic process in the region of the left middle cerebral artery was considered, and steroid therapy resulted in symptomatic and clinical improvement. Once the steroid medication was reduced, however, she developed a left ophthalmoplegia. Magnetic resonance imaging (MRI) revealed a small tumour in the left orbit near the left lateral rectus muscle. Histology of the resected lesion showed necrotizing granulomatous inflammation, with multinucleate giant cells and granulomatous vasculitis (fig. 1). Special stains for fungi and acid and alcohol fast bacilli (AAFB) and culture for tuberculosis proved negative.

Following a differential diagnosis of sarcoidosis or tuberculosis, the patient was treated with steroids, and rifampicin with ethambutol. The antituberculosis therapy was continued for 2 yrs. Attempts to taper off the steroids resulted in return of the headaches and right hemipareses, leading to repeated hospital admissions. On one such occasion in 1989, a routine chest radiograph
demonstrated a rounded opacity in the lower zone of
the right lung and liver function tests proved abnormal:
aspartate amino transferase 254 IU·L⁻¹ (reference inter-
val 5–35 IU·L⁻¹), alkaline phosphatase 171 IU·L⁻¹ (ref-
ence 30–300 IU·L⁻¹), and γ-glutamyl transferase 123
IU·L⁻¹ (reference 7–33 IU·L⁻¹). The appearances of the
liver on ultrasonography was normal. The opacity on
the chest radiograph and the liver function abnor-
malities resolved with increased dexamethasone dosage.

In March 1994, a chest radiograph
revealed a shadow in the right midzone,
and CT scanning suggested a tumour. The
right middle lobectomy specimen revealed
a 4 cm mass of pale homogeneous mate-
rial, with focal haemorrhage surround-
ed by endogenous lipid pneumonia.
The lymph nodes and bronchial resec-
tion margin were normal. Stains for
acid-fast bacilli and fungi (and sub-
sequent culture) proved negative. Histology
of the lesion showed well-defined gran-
ulomata with giant cells, lymphocytes
and plasma cells, aggregated in masses.
Some were related to bronchovascular
bundles. Extensive necrosis was evident
within granulomata and the adjacent
lung parenchyma (fig. 2). The vasculi-
tis, composed of infiltrating lymphocytes
and macrophages, was granulomatous
in some areas. Acute necrotizing vas-
culitis was not identified.

Discussion

For some 20 yrs this patient had fol-
lowed an unusual clinical course, the
exacerbations being partially responsive
to steroid therapy. Auto-antibodies, anti-
cardiolipin antibody, RF, antineutrophil
cytoplasmic antibody (ANCA), hepati-
tis A, B and C serology, and serum an-
giotensin-converting enzyme (ACE)
levels were repeatedly negative. Meas-
urements of ESR and C-reactive pro-
tein (CRP) concentration revealed no
elevation (even during exacerbations of
the syndrome), and her urine was phys-
iological throughout. Testing with Kveim
antigen was never undertaken because
of the continuous therapy with corti-
costeroids. The histology of the orbital
mass was originally described as necro-
tizing granulomatous inflammation with
multinucleate giant cells and granulo-
matous vasculitis, without making reference to the diag-
nosis of necrotizing sarcoid granulomatosis. The right
middle lobe of the lung, resected 12 yrs later, was ex-
amined by a different pathologist, who identified the
histological appearance of necrotizing sarcoid-like gran-
ulomatous inflammation. The biopsy material of the pre-
vious orbital mass was still available and on review
showed identical histology. The long duration of the ill-
ness, its response to steroids, and the negative tissue
cultures make an infectious aetiology unlikely. Wegener's
granulomatosis was excluded on clinical and histopa-
thological grounds.

The relationship between NSG and classical sarcoid-
osis is debatable. CHURG [7] argues that NSG resembles
sarcoidosis histologically, clinically and in the pattern of

Fig. 1. – Granulomatous infiltration in the tissue from the orbit. A small vessel is involved
in the granulomatous process (arrow). Scale bar = 200 µm.

Fig. 2. – As well as showing granulomatous inflammation identical to that in figure one,
the pulmonary lesion revealed parenchymal necrosis bordered by epitheloid cells, giant cells
and chronic inflammation. Scale bar = 500 µm.
NSG WITH EXTRAPULMONARY INVOLVEMENT

extrapulmonary involvement. Histologically however, NSG differs from sarcoidosis in that vasculitis is prominent, necrosis marked, and hilar lymphadenopathy rare. In our patient, lymph nodes and bronchial mucosa were histologically, devoid of disease and there was no evidence of interstitial granulomatous infiltration outside the lesion.

Some of the cases with extrapulmonary disease in the form of hilar node or hepatic involvement referred to by CHURG [7], might have been classical sarcoidosis rather than NSG. The one previously reported case of NSG with extrapulmonary involvement, histologically proven [6], and other cases [3, 7, 8] suggest a predilection for the eye and central nervous system. One patient had ocular symptoms more than 10 yrs before the onset of chest symptoms [4].

NSG may well be related to sarcoidosis, but its clinical and histopathological manifestations would seem to justify its status as a separate disease entity, whether referred to as necrotizing sarcoid granulomatosis or atypical nodular sarcoidosis. Although the illness may be considered benign and responsive to corticosteroids, severe morbidity was experienced by our patient during the protracted clinical course of her disease. At present she remains well on low-dose steroids.

References