Necrotizing Sarcoid Granulomatosis – is it different from nodular sarcoidosis?

**Zusammenfassung**

se entstehen auf dem Boden der granulomatösen Vaskulitis mit progredientem Gefäßverschluss. Ob dies die Folge einer länger-
dauernden Vaskulitis mit Lungenobstruktion darstellt, kann
letztendlich noch nicht beantwortet werden. Basierend auf unse-
ren Untersuchungen und den vorhandenen Literaturdaten sollte
die NSG am besten als Variante der nodulären Sarkoidose inter-
pretiert werden. Im Gegensatz zu unseren Erfahrungen bei Sar-
koidose konnte bei keinem der Patienten eine myokbakterielle
DNA nachgewiesen werden.

Introduction

Necrotizing sarcoid granulomatosis (NSG) was initially separated
as an entity by A. Liebow [1]. In his initial cases only lung invol-
vement was found. The morphologic features of NSG were consi-
dered in between sarcoidosis and Wegener’s granulomatosis
(WG). The cases showed granulomatous vasculitis and nodular
aggregates of epithelioid cell granulomas with foci of central ne-
crosis. No organisms could be found. In subsequent years other
reports have shown involvement of non-pulmonary organs, na-
mely eyes, liver, and spleen [2 – 6]. In addition nodular sarcoido-
sis has become recognized as a variant of sarcoidosis [7], and
those cases showed an overlap with NSG. Since the introduction
of video-assisted thoracoscopic and the resultant larger than
transbronchial biopsy specimen granulomatous vasculitis is
more often seen in sarcoidosis, which again eliminates one fea-
ture, thought to be characteristic for NSG [8].

We therefore undertook a study of NSG and compared the fea-
tures of NSG with sarcoidosis. We specifically looked for features
which might unequivocally differentiate NSG from nodular sar-
coioidosis. Since we found mycobacterial DNA in some of our sar-
coioidosis cases [9] we assumed that necrosis found in NSG might
be associated with a positivity for mycobacterial DNA. Therefore
all cases were investigated for mycobacterial DNA using PCR.

Methods and Materials

Slides and paraffin blocks from lung lesions were retrieved from
the archives of three Institutions. Cases fulfilling the criteria of
NSG were selected by the authors: nodular aggregates of epite-
hioid cell granulomas, necrosis, and granulomatous vasculitis, and
the absence of identifiable infectious etiology by culture and/or
special stains. Only ten cases which fulfilled these criteria were
collected. H & E and Movat pentachrome stained sections and
acid fast stains were made from formalin fixed paraffin embed-
ded lung tissue blocks. DNA was extracted from paraffin sections,
and a PCR for the mycobacterial chaperonin and for the insertion
sequence (IS) 6110 was done exactly as described previously [9].
Appropriate negative and positive controls cases were included.

Organ involvement other than pulmonary in these cases were:
ocular in 1, liver in 2, spleen in 1, and hilar and mediastinal
lymph nodes in 2 cases. In all these cases non-pulmonary in-
volvement was confirmed either by tissue biopsy or CT scan
(Table 1).

<table>
<thead>
<tr>
<th>Age</th>
<th>Sex</th>
<th>Lung involvement</th>
<th>Extrapulmonary involvement</th>
<th>Unrelated disease</th>
</tr>
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<tbody>
<tr>
<td>42</td>
<td>M</td>
<td>single nodule, OL</td>
<td>ocul a r</td>
<td></td>
</tr>
<tr>
<td>42</td>
<td>F</td>
<td>2 nodules, OL</td>
<td>liver, spleen</td>
<td></td>
</tr>
<tr>
<td>45</td>
<td>M</td>
<td>single nodule, OL</td>
<td>no</td>
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<td>F</td>
<td>3 nodules, OL</td>
<td>pleura, liver</td>
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<tr>
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<td>F</td>
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<td>no</td>
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</tr>
<tr>
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<td>na</td>
</tr>
<tr>
<td>28</td>
<td>M</td>
<td>nodules, OL</td>
<td>no</td>
<td>pleuritis, fever</td>
</tr>
<tr>
<td>12</td>
<td>M</td>
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<td>no</td>
<td>glomerulonephritis, pleuritis, dead due to pneumococcal sepsis*</td>
</tr>
<tr>
<td>66</td>
<td>M</td>
<td>bilateral basal</td>
<td>no</td>
<td>na</td>
</tr>
<tr>
<td></td>
<td></td>
<td>nodules (limited</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>autopsy)</td>
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</tbody>
</table>

* In this case primarily there was a differential diagnosis of hypersensitivity pneumonia, Wegener’s granulomatosis, infectious granulomatosis, necro-
tizing sarcoid granulomatosis. All former three were excluded clinically and
by special stains and culture

For comparison six cases of nodular sarcoidosis, characterized by
nodular aggregates of epithelioid cell granulomas from 4 mm to
3 cm in diameter were chosen from the files of the authors (HHP).

Results

In all cases granulomatous nodules and large areas of necroses
could be found. In serial sections the contributing pulmonary
arteries were demonstrable, all showing different stages of grani-
lomatous vasculitis. The lumina of these arteries were either nar-
rowed or completely obstructed by multiple epithelioid cell granu-
lonomas. At the very early stages an infiltrate of lymphocytes,
macrophages, few epithelioid and Langhans giant cells without
granulomatous organization could be found (Fig. 1), in later
stages mature confluent epithelioid cell granulomas predominat-
ed, leading to partial or total lumen obstruction (Fig. 2 – 4). In very
late stages the vessel lumina were completely obstructed and only
remnants of the inflammatory infiltrate could be found (Fig. 4).
Middle sized as well as small sized blood vessels were involved.
Necrotic areas were always found around this vasculitis. In all ca-
ses non-necrotizing large nodular aggregates of epithelioid cell
granulomas were seen in the lung parenchyma (Fig. 5). The
amount of Langhans giant cells was variable, ranging from a few
to numerous cells. Lung involvement including hilar lymph nodes
was present in all cases, whereas extravascular involvement was
documented in three cases, including ocular liver and spleen.

Mycobacterial DNA, neither mycobacterial chaperonin, nor in-
sertion sequence 6110 was not found in any of the 10 cases.

In nodular sarcoidosis similar large aggregates of epithelioid cell
granulomas as in NSG were seen and also granulomatous vascular
involvement (Fig. 6). The only difference was the absence of necrosis and
vascular lumen obstruction in nodular sarcoidosis.
Fig. 1 Granulomatous vasculitis in NSG with epitheloid cell granulomas. In this early stage there is no obstruction of the vascular lumen; H & E, original magnification × 100.

Fig. 2 Granulomatous vasculitis in NSG with epitheloid cell granuloma (upper left). In this late stage vascular lumen is partially obstructed and there is some recanalization; Movat pentachrome, original magnification × 65.

Fig. 3 Granulomatous vasculitis in NSG. The lumen of this large pulmonary artery is partially obstructed, smaller arteries in the surrounding infarct-like necrosis, however, are complete occluded. Epitheloid cell granulomas can be seen within but also outside this necrotic focus. Movat pentachrome, original magnification × 40.

Fig. 4 Late stage of vasculitis: This small pulmonary artery is completely obstructed, remnants of the elastic laminae are visible, but only a few inflammatory cells. The surrounding lung parenchyma is completely necrotic. Movat pentachrome, original magnification × 100.

Fig. 5 Nodular aggregates of epitheloid cell granulomas in NSG. H & E, original magnification × 65.

Fig. 6 Granulomatous vasculitis with epitheloid cell granulomas in a case of nodular sarcoidosis; there is no lumen obstruction of this small vein; H & E, original magnification × 100.
Discussion

NSG was originally defined by Liebow as a lung specific granulomatous disease with vasculitis and necrosis, lying in between sarcoidosis and Wegener’s granulomatosis – hence the name [1]. Subsequent reports have shown that NSG is a systemic disease with extrapulmonary involvement. Most often pleural, ocular, liver and spleen lesions were described [2–6].

The invention of video-assisted thoracoscopy has opened the opportunity to review larger lung specimens in sarcoidosis too. This has enabled us to see granulomatous vasculitis in sarcoidosis more often, than anticipated from our experience with transbronchial biopsies and equals that seen in autopsy cases [8], and nodular sarcoidosis, a variant of sarcoidosis with larger, macroscopically visible nodular aggregates of epithelioid cell granulomas is seen more often. This has brought up the question, if NSG is another variant of sarcoidosis.

This has prompted us to retrieve cases from our institutional collections and to compare the features with those of nodular sarcoidosis (NS). Nodular aggregates of epithelioid cell granulomas are found in NSG and in NS. Granulomatous vasculitis too can be seen in NSG and NS, however, complete obstruction of the vascular lumina was only seen in NSG. And necrosis is still the hallmark of NSG. There is a coagulative infarct-like type of necrosis in NSG, which could in most of our cases be attributed to the granulomatous vasculitis with lumen obstruction. Therefore it might be speculated, that NSG is the late stage of NS, when vascular lumen obstruction has occurred and in turn caused infarct-like necrosis. Much rarer necrosis might also be caused by the confluence of degenerative fibrinoid necrosis, sometimes also seen as necrobiotic foci in sarcoidosis.

In addition clinical investigations and comparative clinico-pathologic studies have shown similar immunologic features for NSG and sarcoidosis, for example a dominance of T-helper lymphocytes and a T-helper associated cytokine spectrum in BAL fluid ([10–12]; and personal unpublished observations).

In the differential diagnosis Wegener’s Granulomatosis can easily be discerned by the presence of granulocytic vasculitis in the early and lymphocytic vasculitis in the late phase. Bronchocentric granulomatosis can be differentiated from NSG by the absence of a granulomatous vasculitis and infarct-like necrosis, and lymphomatoid granulomatosis (angiocentric high grade non-Hodgkin lymphoma) by a vascular infiltrates composed of highly atypical lymphoid cells.

In contrast to previous findings in sarcoidosis, none of the NSG cases had an association for mycobacterial DNA [9], ruling out a Mycobacteria based etiology.

In our opinion NSG should be classified as a variant of sarcoidosis, characterized by extensive granulomatous vasculitis, which in turn causes coagulative necrosis. NSG do no longer qualify as a separate entity.

References

1 Liebow AA. The J. Burns Amberson Lecture: Pulmonary angiitis and granulomatosis. Am Rev Respir Dis 1973; 108: 1
3 Churg A. Pulmonary angiitis and granulomatosis revisited. Hum Pathol 1983; 14: 868
7 De Remee RA. Sarcoidosis and Wegener’s granulomatosis: a comparative analysis. Sarcoidosis 1994; 11: 7–18