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Membranocystic lesions of the lung in Nasu-Hakola disease

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Summary. Massive membranocystic lesions of the lung were found in an autopsy case of Nasu-Hakola disease. The membranocystic structures are virtually identical to those found in adipose tissue, including bone marrow. Capillary endothelia and alveolar epithelial lining cells do not participate in membranous structure formation, these structures being found in the alveolar septa and not apparently of an embolic nature. They may be related to alveolar septal cells in a broad sense. The pathogenesis of this disease is discussed in relation to the lesions of the lung.

Key words: Nasu-Hakola disease – Membranocystic lesion – Pulmonary involvement – Electron microscopy

Nasu-Hakola disease is a new nosological entity which is characterized by membranocystic lesions in systemic adipose tissue, including bone marrow, and leucoencephalopathy of the brain. This very rare disease has been reported mostly in an isolated region of Finland and in Japan, and termed "progressive dementia with membranous polycystic osteodysplasia" in Finland (Hakola et al. 1972) and "membranous lipodystrophy of Nasu" or "Nasu-Hakola disease" in Japan (Nasu et al. 1970, 1973; Matsushita et al. 1981).

The characteristic membranocystic lesion has been reported exclusively in adipose tissue and bone marrow and very rarely in the other organs. In this communication, we will report primary pulmonary involvement in Nasu-Hakola disease; massive membranocystic lesions in the alveolar walls of the lung, with speculation on the possible nature of this disease.

Case report

The male patient was 36-year-old when he entered our hospital. The family history was noncontributory. Since the age of 16 he had suffered fractures in connection with minor accidents

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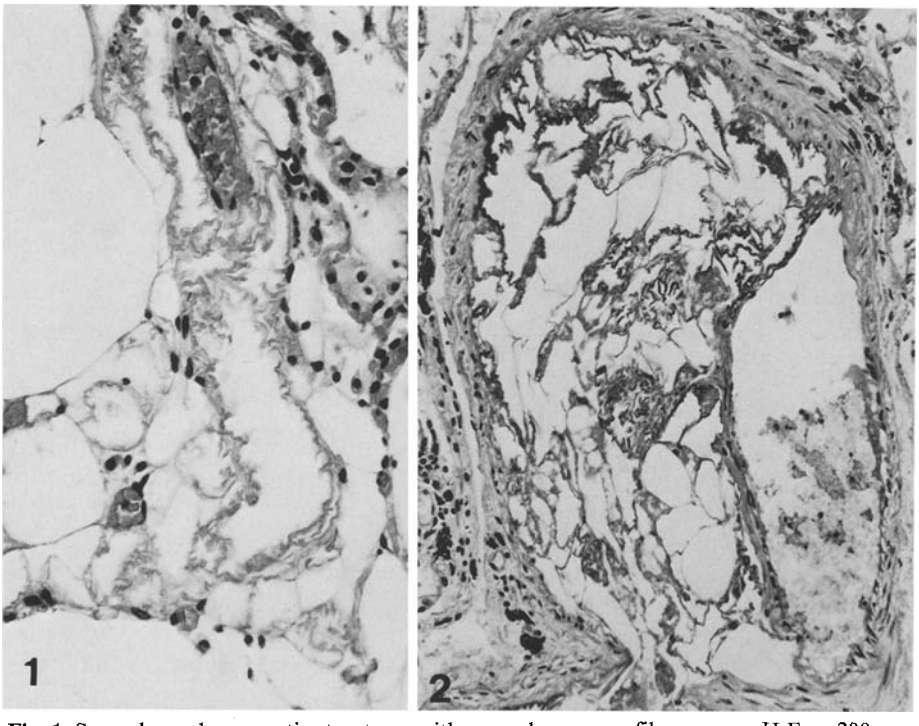

Fig. 1. Several membranocystic structures with an arabesque profile are seen. H.E. × 200

Fig. 2. Massive membranocystic structures in the wall of a small blood vessel. PAS. × 200

and was diagnosed to have fibrous dysplasia of bone. On admission, X-rays revealed multiple cystic changes of the bone, sparing the ribs, cranium, pelvic bones and spinal column. The patient was mentally retarded and neurological examination suggested a degenerative disease of the white matter of the brain. Bone marrow and skin biopsies showed massive characteristic membranocystic changes, and a diagnosis of membranous polycystic osteodysplasia was made (Yagishita et al. 1977). The patient gradually deteriorated and suffered frequent attacks of grand mal epilepsy. Death ensued at the age of 44 years.

The autopsy confirmed Nasu-Hakola desease (Nasu et al. 1973; Harada 1975; Tanaka 1980): There were extensive membranocystic changes in adipose tissue including the intra-abdominal and pleural fat as well as the bone marrow. The brain showed leucoencephalopathy with many axonal swellings and spheroidal bodies (the neuropathological findings will be described elsewhere).

Histopathology of the lung

Each lung weighed 550 g. (left) and 400 g. (right) and showed congestive oedema and was elastic and firm in consistency. Histologically, the lungs revealed peculiar lesions; numerous undulating membranous structures formed tiny cysts with an arabesque profile. At a first glance, the membranes appeared to encircle alveolar spaces, as the hyaline membranes in hyaline membrane disease do. They were palely eosinophilic with haematoxylin-eosin (Fig. 1). The histochemical properties of the membranes are virtually identical to those of adipose tissue and bone marrow, as previously reported (Yagishita et al. 1977). They were PAS-positive (Fig. 3) and sudanophilic (Fig. 4). Very rarely, the membranous structures were found within the vascular wall, mostly in small arteries (Fig. 2)

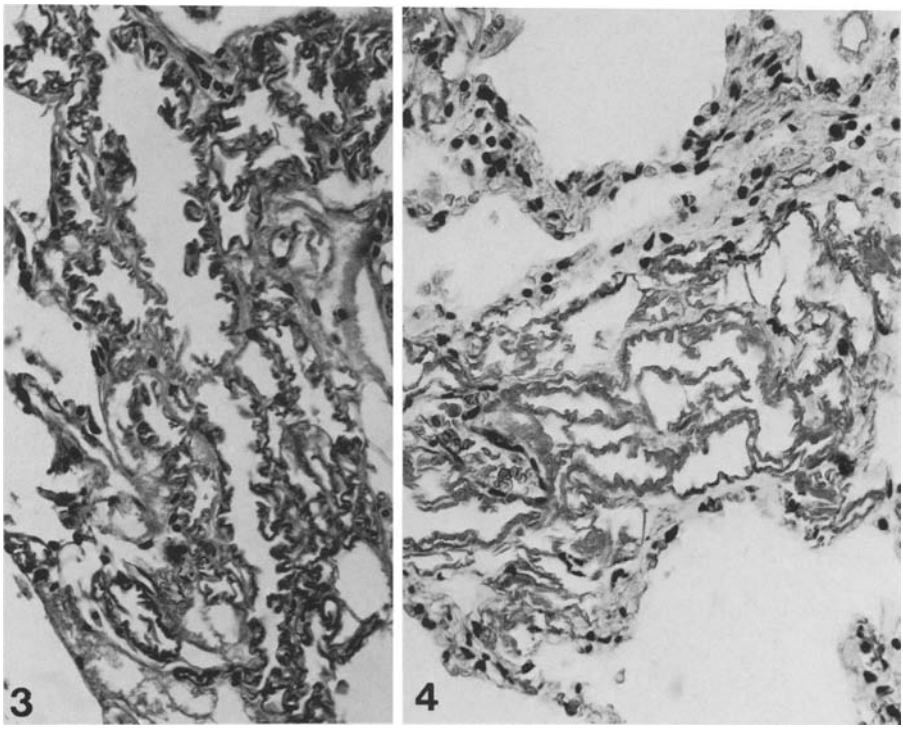

Fig. 3. The membranes are positive for PAS. × 200

Fig. 4. The membranes are sudanophilic even in a paraffin-embedded section. Sudan III. × 200

Electron microscopic study

Small samples were taken from the lung which was stored in 10% formalin solution for about one month. The small pieces were fixed in 2.5% glutaraldehyde, post-osmificated, dehydrated in graded alcohol and embedded in epon mixture. The semi-thin sections were polychromatically stained and selected for electron microscopic examination.

The semi-thin sections also showed membranous cystic lesions, the cystic spaces of which contained homogeneous and osmiophilic globules presumably neutral fat droplets (Fig. 6 Inset).

The tissue preservation is poor for non-buffered 10% formalin fixation, however, some interpretation could be made. The membranes seen under light microscopy consisted of complicated membranous structures under electron microscopy, the inner side of which was smoothly demarcated by an electron dense line encircling moderately electron dense homogeneous substance corresponding to neutral fat. Numerous minute tubular structures projected to the outer side which provided to be the interstitum, where collagen and elastic fiber bundles frequently identified. Some of the membranes lacked tubular projections and instead had a strikingly crenated surface (Figs. 5 and 7). The picture is virtually identical to the membranocystic structures previously reported in adipose tissue and bone marrow.

As the tissue preservation was poor and the plasmalemma of the majority of the cells was destroyed, the precise location of the membranous structures could not be assessed. However, they were always located within the area enclosed at least by capillary and epithelial basal laminas (Figs. 6 and 7). They had no intimate relationship with alveolar epithelial lining cells or capillary endothelial cells. Collagen and elastic fiber bundles were seen in the vicinity of the membranous structures (Fig. 6). Some undetermined cells and macrophages were occasionally seen in the alveolar septa.

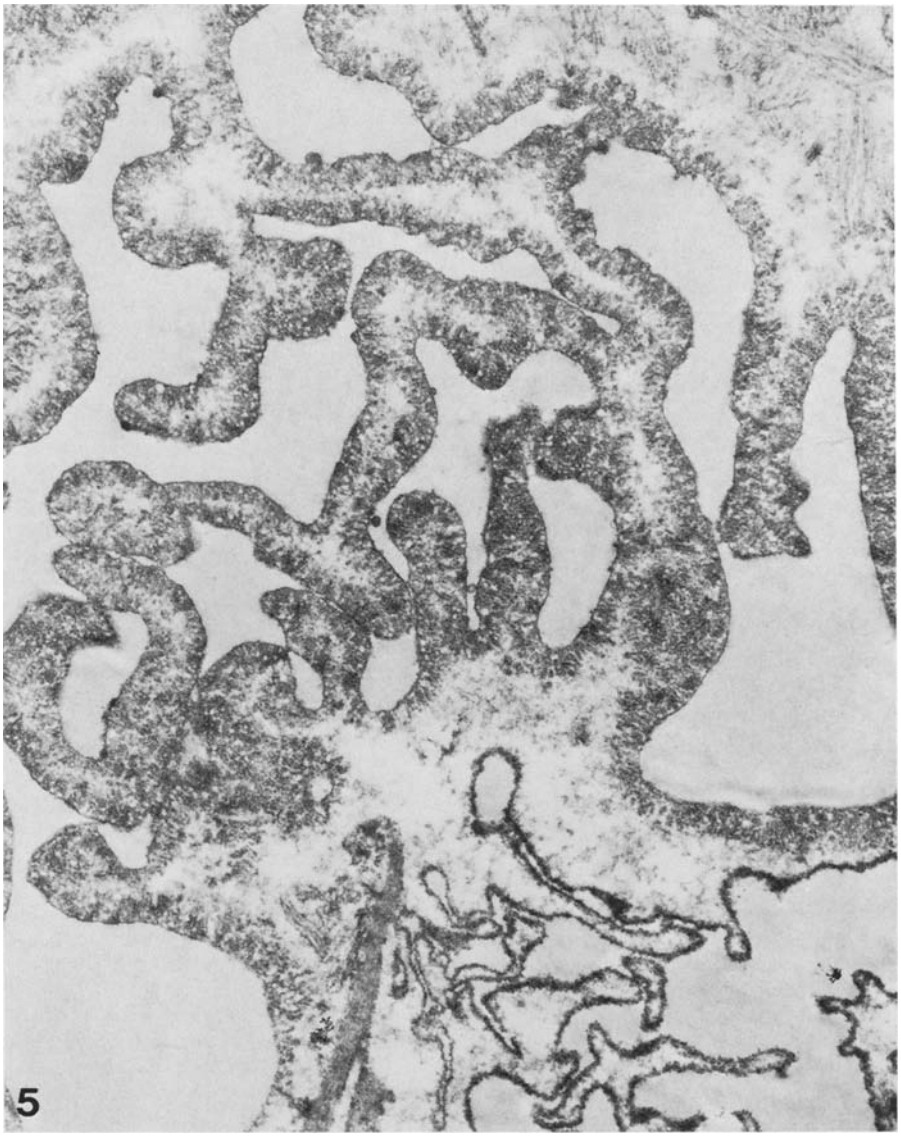

Fig. 5. The membranes consist of complicated membranous structures. Its inner side is smoothly demarcated by an electron dense line encircling neutral fat and countless minute tubular structures project to the outer side. The membranes (*lower right*) have a crenated surface. × 8,000

Discussion

The present case has the typical findings of membranous lipodystrophy. Membranocystic lesions are thought to occur exclusively in adipose tissue, including bone marrow, since the target cell in this disease seems to be only mature or immature fat cells. The common findings observed in the central nervous system (CNS) represent a leucoencephalopathy in the broad

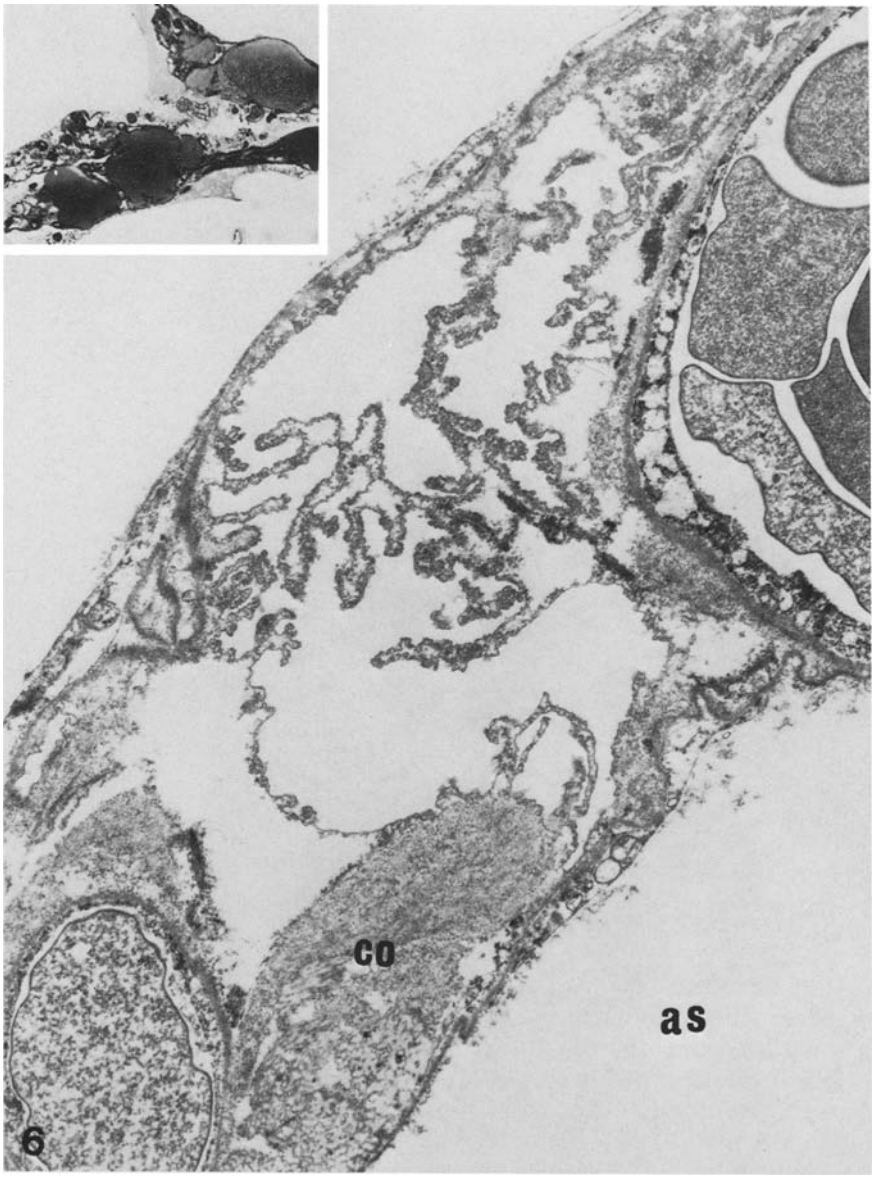

Fig. 6. Membranous structures are seen within the alveolar septa. ×12,000 as: alveolar space, co: collagen fibrils. *Inset*. Several osmiophilic globules are seen in alveolar walls. Epon-embedded semi-thin section. ×200

sense, but no membranocystic changes can be found. As in the CNS, the visceral organs without fat cells are not usually involved in the membranous lipodystrophic process. Only Nasu et al. (1973) wrote "The substance was present focally at places in the lung and liver, but not apparently within the cells and limited amount generally" without further documentation. As the substance in the lung seemed to be present in vascular lumena,

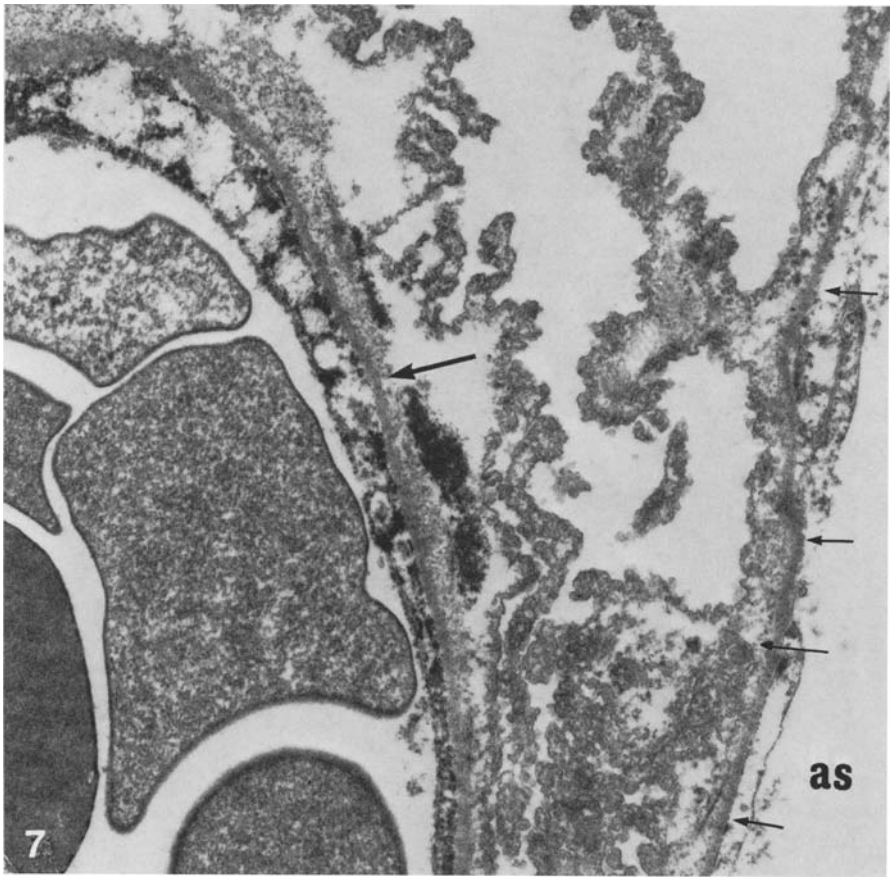

Fig. 7. Higher magnification of Fig. 6. Membranous structures are seen between capillary and alveolar epithelial basal laminas. × 6000

it was considered to be of an embolic nature from bone marrow lesions (Nasu, personal communication).

In this case, the pathology of the lung showed peculiar lesions hitherto undescribed; massive membranocystic structures virtually identical to those in adipose tissue. Many neutral fat droplets were found encircled by a inner smooth dense line while on the outer side microtubular structures projected into the interstitium. The membranous structures were apparently located within the alveolar septa as shown in Figs. 6 and 7, and had no intimate relationship with alveolar epithelial lining cells or capillary endothelia.

The pathogenesis has not been clarified because of the rarity of this disease. Jarvi (1970) considered that necrosis of blood vessels was responsible for the bone lesion, and Nasu et al. (1973) suggested an inborn error of the metabolism of fat cells which induced membranous transformation in various organs and caused sudanophilic leucodystrophy in the brain.

Most cells of the intra-alveolar walls are endothelial cells of the capillaries and epithelial cells that line alveoli. The second kind of cell is the alveolar

(septal) cell and two types are described, the vacuolated lipoid-containing and the non-vacuolated varieties. Some macrophages are also occasionally seen here (Ham, 1965). Tashiro et al. (1976) suggested that the membranous structures derived from abnormal proliferation of fat cell plasma membrane. If this is true, although no nuclei were found in relation to the membranous structures in all cases reported, these should be derived from alveolar septal cellls in a broad sense. Therefore, it is suggested that there may be not only an abnormality of lipid metabolism of mature fat cells but also an abnormal differentiation of target cells. In this case, the abnormal process of differentiation from primitive mesenchymal cell to fat cell in the alveolar septum might play a possible role in membranous structure formation. This notion should be explored to elucidate the pathogenesis of this disease.

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