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Polymorphic Reticulosis (Lethal Midline Granuloma) and Lymphomatoid Granulomatosis: Identical or Distinct Entities?

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Summary. Two cases of polymorphic reticulosis were studied. Both cases had a fatal clinical course, that of the second case being rapid and progressive and ending 6 months after the onset of the disease with little demonstrable effect of steroid therapy. Biopsy material was obtained in both patients, and both were submitted to a post-mortem examination. The first case showed typical angiocentric, angiodestructive, polymorphous lymphoreticular infiltrates, involving the pharyngeal region and the tongue. The second case demonstrated these same lesions in the midfacial region, the lungs and the skin. A possible identity between polymorphic reticulosis and lymphomatoid granulomatosis is discussed (because of the coexistance of identical lesions in the midfacial region and in the lung parenchyma in the second case). Wegener's granulomatosis in limited and disseminated forms and malignant lymphoma are considered in the differential diagnosis.

Key words: Midfacial – Lung – Lethal granuloma – Lymphomatoid granulomatosis – Reticulosis.

Introduction

Lethal midline granuloma is a clinical term used to label midfacial, infiltrative and destructive granulomatous lesions with a malignant evolution. It includes three different entities, i.e., Wegener's granulomatosis, polymorphic reticulosis and malignant lymphoma of the midfacial region (Kassel et al. 1969; DeRemee et al. 1978).

Liebow et al. (1972) first described lymphomatoid granulomatosis of the lung (LYG). This newly introduced clinicopathological entity was then included among the group of conditions known as pulmonary angiitis and granulomatosis (Liebow 1973). The disease is characterized by angiocentric, angiodestructive,

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lymphoreticular proliferative and granulomatous lesions predominantly involving the lungs, commonly sparing lymph nodes and the bone marrow, but often with associated lesions in the skin, central nervous system, the kidneys, adrenal glands and sometimes the digestive tract. Cases have been reported of involvement of extrapulmonary tissues in the absence of lung disease (Chen 1977; DeRemee et al. 1978).

Striking histopathological similarities between polymorphic reticulosis and lymphomatoid granulomatosis have led Douglas et al. (1976), DeRemee et al. (1978), Crissman (1979) and others to the conclusion that they are the same disease process.

Two cases are presented in this report, one with lesions involving the midfacial region only, and the other having an association of identical lesions in the midfacial region with lung and skin lesions.

Case Reports

Case No. 1

Clinical Findings

A 73 year-old woman was admitted to the neurology ward at the University of Geneva Cantonal Hospital because of pain along the course of the right trigeminal ophthalmic nerve branch and right hypoacousia. She had no significant medical history, but complained of palpitations and dyspnoea for several years. Five months prior to admission, she developed chronic hiccups, dysphagia, anorexia and weight loss. Physical examination revealed an elderly woman in good general condition. The temperature was 37° C, the pulse 80, blood pressure 140/80 and respiratory rate 18. Cardiovascular, pulmonary and abdominal examinations were negative. Neurologic examination revealed compression of the Vth, VIth, VIIth, VIIIth, IXth, XIth and XIIth right cranial nerves by a tumour infiltrating the entire right base of the skull. Skull X-rays disclosed proliferative and sclerosing infiltrates involving the petrous part of the temporal bone, the greater wing of the sphenoidal bone, the foramen ovale and the foramen spinosum on the right (Fig. 1).

A right temporal trepanation was performed and an exploration disclosed no tumour mass. The epipharynx disclosed necrotizing ulcerated lesions, and a biopsy within this region showed polymorphocellular, infiltrative lesions, and the diagnosis of polymorphic reticulosis was made. Radiation therapy was administered at a dose of 4,000 rads of telecobalt. The treatment was well tolerated and, as a result, considerable regression of the neurologic symptoms was observed, with improvement of deglutition, the palatine and pharyngeal reflexes becoming almost symmetrical.

The patient was discharged and was admitted 7 months later for pyrosis, dysphagia, vocal changes, weight loss and hypotension. Physical examination revealed a woman in poor general condition with facial telangiectasias and right conjunctival hyperaemia. Cardiovascular examination disclosed compensated congestive heart failure. Pulmonary and abdominal examinations are negative. Laryngoscopy showed extension of the pharyngeal lesions which were necrotizing, ulcerated and infected. The C.T. scan of the brain demonstrated an extension of the lesions seen previously, toward the right. The patient developed bronchopneumonia and died 5 months later, despite a second course of radiation therapy and antibiotics.

Pathology

Biopsies. The two initial fragments from the epipharynx were embedded in paraffin-wax and stained by H & E. They revealed a squamous mucosa with an ulcerated epithelium beneath which there was a nodular, granulomatous lesion. This lesion was composed of a mixture of lymphocytes, plasma cells,

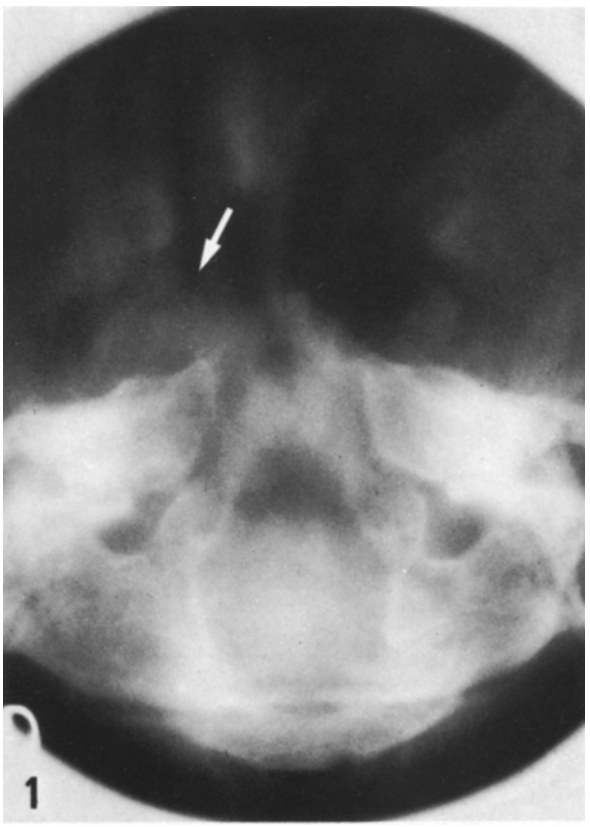

Fig. 1. Case 1. Skull X-ray: infiltration of the right part of the sphenoidal bone (*arrow*) is shown

neutrophils and eosinophils, as well as numerous large histiocytes. These histiocytes showed nuclear pleomorphism with occasional mitotic figures (Fig. 2). A reticulin stain showed the presence of a fine collagen network between the mononuclear cells with, in addition, a perivascular disposition. The infiltration had a nodular appearance involving and destroying the mucus membrane and the muscle fibers (Fig. 3). In view of the character of the lesion and the absence of necrotizing vasculitis, the diagnosis of polymorphic reticulosis was proposed.

Post-Mortem Examination. Autopsy confirmed the absence of systemic dissemination of the lesions. A necrotic and purulent mass had developed in the right nasal cavity, infiltrating posteriorly the right infero-external surface of the base of the skull, and extending toward the middle ear. A downward extension was discovered toward the epipharynx and the base of the tongue. The tongue presented a smooth surface, with loss of papillae and an ulcerated lesion of 1 cm in diameter in the region of the lingual V, with a small whitish, round mass. A cross-section revealed several other ulcers around the lingual base and the epipharynx. The cranial nerves were, however, free of lesions along their intracranial course.

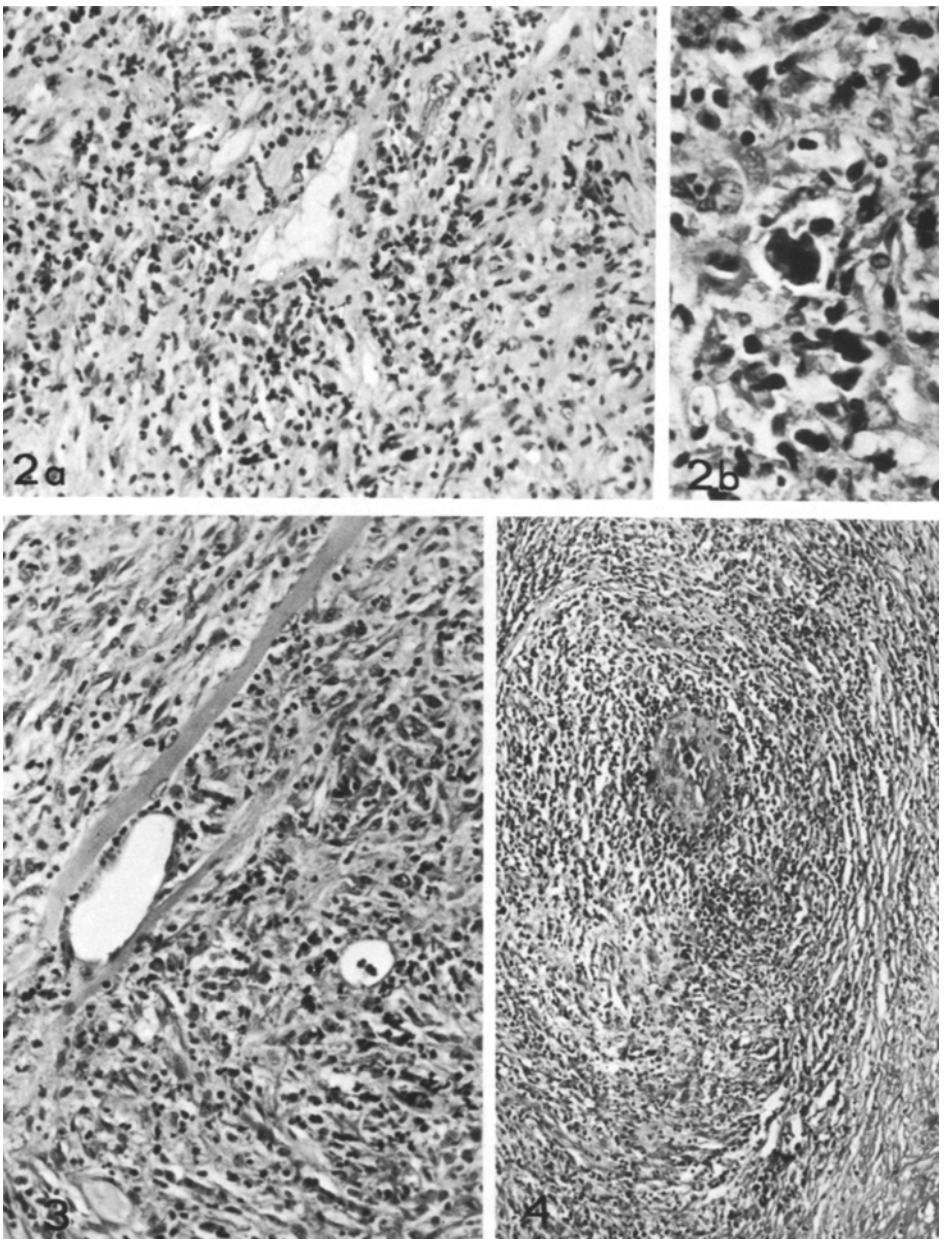

Fig. 2a and b. Case 1. Epipharynx biopsy: **a** Note the polymorphic infiltrate composed of lymphocytes, plasma cells, neutrophils, eosinophils and of atypical histiocytes. In the center, there is a venule (H.E. ×480), **b** Atypical histiocytes with hyperchromatic irregular nuclei, without erythrophagocytosis (V.G.E. ×1,200)

Fig. 3. Case 1. Epipharynx biopsy: polymorphic cell infiltrate dissociating and destroying the striated muscle fibers is visible (V.G.E. ×480)

Fig. 4. Case 1. Autopsy material (tongue). Note the angiocentric angiodestructive features of the lesion

Histology of the lingual lesions showed numerous ulcerations of the mucosa by granulomatous, nodular infiltrate penetrating deeply into the muscular layer with partial destruction of the latter. The same polymorphism of cells was observed as in the initial biopsies, but in addition there was an angiocentric disposition with, occasionally, destruction of arteries or veins (Fig. 4). The rest of the autopsy revealed no other location of these lesions.

Case No. 2

Clinical Findings

A 41 year-old patient of Tunisian origin was admitted for frequent episodes of rhinitis with a sensation of obstruction of the nasal passages. His medical history included typhoid fever 29 years previously.

Five months earlier, he had a partial resection of the nasal septum, with the diagnosis of "obstruction of the nasal passages with infiltration of the septum". Histological examination had not been performed. A chest X-ray at the time had been considered as "normal".

Repeated X-rays of the nasal passages showed irregular opacities within the remaining septum, and a biopsy in that region revealed necrotic material with lymphocytic and plasma cell infiltration, but no cytological signs of malignancy. He complained of dyspnoea and a chest X-ray disclosed round, nodular lesions, a few mm to 2 cm in diameter, disposed irregularly on both lung fields, but with a greater concentration toward the lower lobes. He was refered to the Geneva University Cantonal Hospital with the diagnosis of Wegener's granulomatosis.

On admission, clinical examination revealed a tachypnoeic patient (40/min) in poor general condition. His temperature was 39.6° C, his pulse 152/min, his blood pressure 130/90. There were no palpable peripheral lymph nodes. Round, purple, macular cutaneous lesions were visible on the anterior trunk. Cardiovascular examination was negative. Pulmonary examination revealed diffuse, fine rales over both lung fields. Ear-nose-throat examination showed sero-sanguinous nasal lesions and ulceration of the palate. Biopsies of the lesions led to the initial diagnosis of lethal mid-line granuloma. On the following day, cutaneous and pulmonary transbronchial biopsies were obtained showing identical lesions. On the basis of these findings, the diagnosis of lymphomatoid granulomatosis was made. The rest of the physical examination was negative.

An admission chest X-ray confirmed the presence of nodular infiltrates in both lung fields with confluence toward the bases (Fig. 5). Arterial blood showed a pO_2 of 51 mm Hg, a pCO_2 of 35 mm Hg and a pH of 7.49. Haematocrit was 47%, haemoglobin 10.2 g % and the white blood count (WBC) 11,250 with 27% band forms. The platelet count was 428.000. Creatinine was 0.8 g/100 ml and the BUN was 18 g/100 ml.

The patient remained hypoxic despite an inspiratory O_2 fraction of 40%. A transparietal pulmonary needle biopsy showed the presence of *Pneumocystis carinii*.

Trimetoprim-sulfamethoxazole was begun intravenously, and the patient was intubated. A combined therapy consisting of Vincristine and Cyclophosphamide was started, and Prednisone was added at the rate of 125 mg/day. The pO_2 nevertheless remained low, oscillating between 49 mm Hg and 51 mm Hg, and the patient was placed on PEEP. However, no significant improvement was noted in terms of respiratory gases.

On the 13th hospital day, spiking fever developed and thick, greenish secretions appeared. A Gram stain of the sputum revealed numerous Gram-negative rods which were shown to be *Pseudomonas aeruginosa*. The patient died a few hours later.

Pathology

Biopsies. Repeated biopsies of the nasal cavity revealed proliferations of large reticulo-histiocytic cells with occasionally two nuclei and a large number of mitotic figures. A few "normal" appearing lymphocytes and plasma cells were

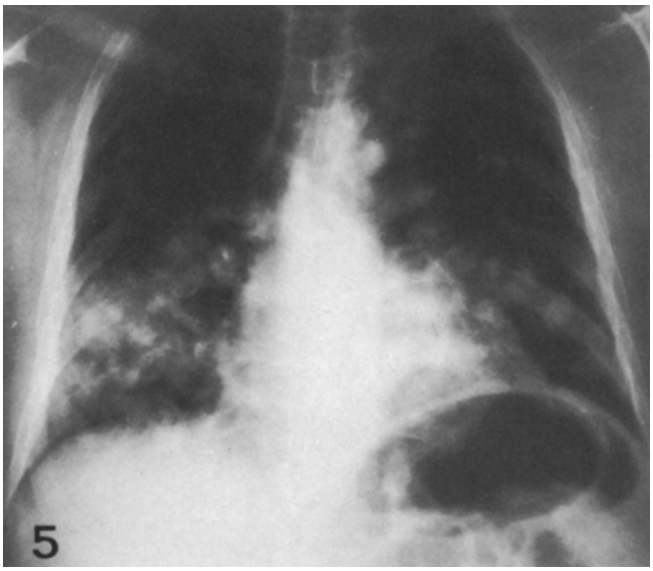

Fig. 5. Case 2. Chest X-ray: shows bilateral basal nodular pulmonary infiltrates with confluence in the right lung

seen. The surface epithelium was ulcerated and necrotic, and beneath it, were two arteries with walls infiltrated and partly destroyed by the cells described above. A reticulin stain disclosed a very fine network of collagen between the reticular cells. A PAS stain showed that glands were intact, the infiltrate penetrating between them (Fig. 6). No signs of vasculitis were seen.

The transbronchial pulmonary biopsy revealed a dense cellular infiltrate in masses with arteries and veins at their center. There was an absence of vasculitis. The infiltrate consisted of numerous histiocytes, many of which showed mitotic figures, plasma cells, lymphocytes and lymphoblasts. One venule was partly destroyed.

The skin biopsy showed a dense infiltrate identical to that described above; angiocentricity was, however, not marked, and once again there was absence of vasculitis (Fig. 7).

Post-Mortem Examination. The nasal cavity revealed bilateral necrotic and ulcerated lesions, destroying the septum. Some lesions appeared as whitish nodules, a few mm in diameter.

Gross pulmonary examination showed the presence of several whitish nodules of roughly spherical shape and firm consistency, dispersed across the parenchyma of both lungs. Some were sub-pleural and others were located deep within the parenchyma. The size of the nodules varied between 0.5 cm and 2.2 cm, some having a necrotic and excavated center. Apart from the skin, there was no dissemination of these nodules to other organs, in particular to the liver, spleen or lymph nodes.

Histologically, the nasal and skin lesions were similar to those described in the biopsies. The lung lesions were characterized by dense cellular infiltrates

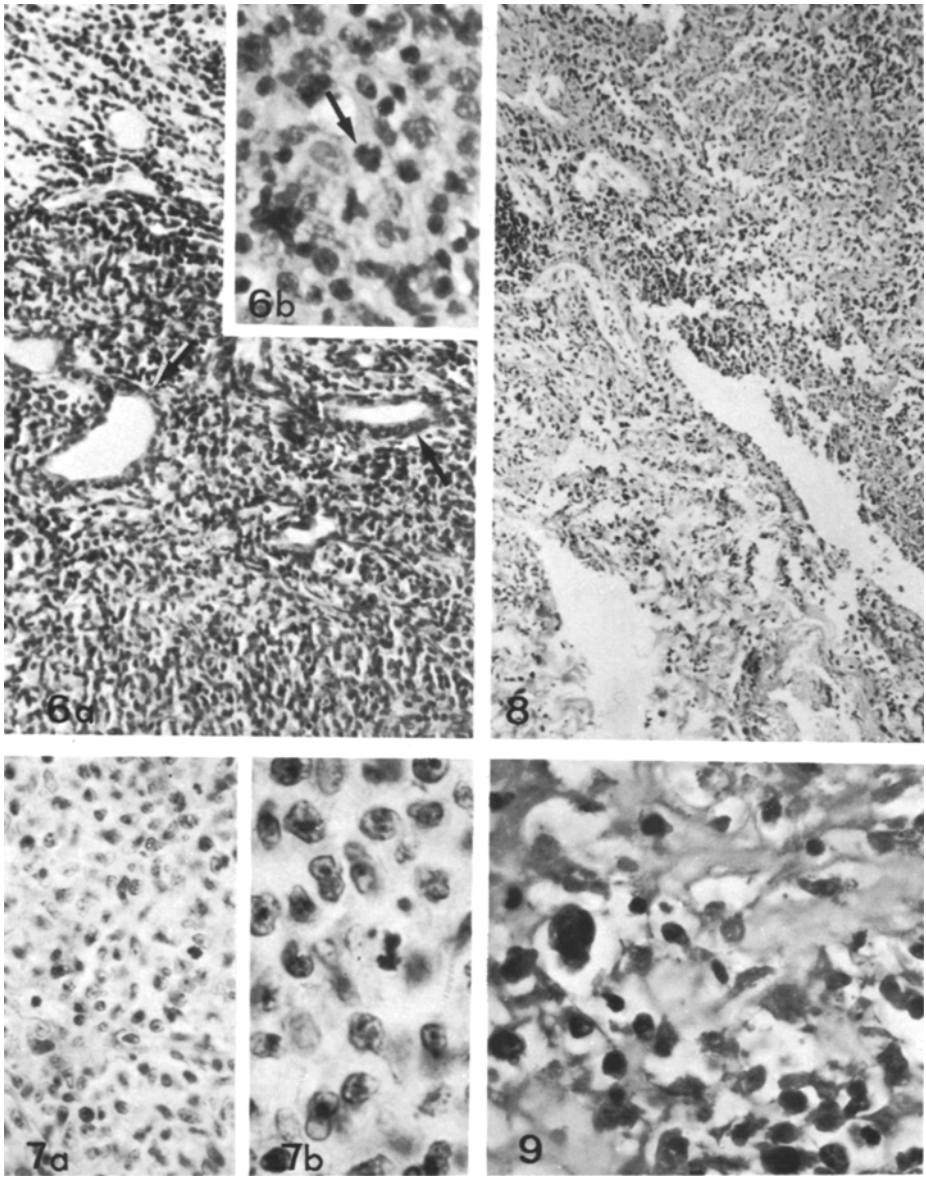

Fig. 6a and b. Case 2. Nasal cavity biopsy: **a** A dense polymorphic infiltrate sparing glands (*arrows*) is visible (H.E. ×200), **b** This infiltrate is composed of lymphocytes, plasma cells, neutrophils and atypical histiocytes with mitotic figures (*arrow*) (H.E. ×1,200)

Fig. 7a, and b. Case 2. Skin biopsy: **a** A dense polymorphic infiltrate composed of cells is shown (H.E. ×480), **b** At high magnification, numerous atypical histiocytes with large nucleoli and occasional mitotic figures are recognized (H.E. ×1,200)

Fig. 8. Case 2. Autopsy material: Periphery of the lung infiltrate is shown. The features of the cells are similar to those at other locations (see also Fig. 9); the alveolar pattern is completely obscured, the septa being destroyed (H.E. ×125)

Fig. 9. Case 2. Autopsy material (lung): Large atypical histiocytes mixed with lymphocytes and plasma cells within an infiltrate (H.E. ×1,200)

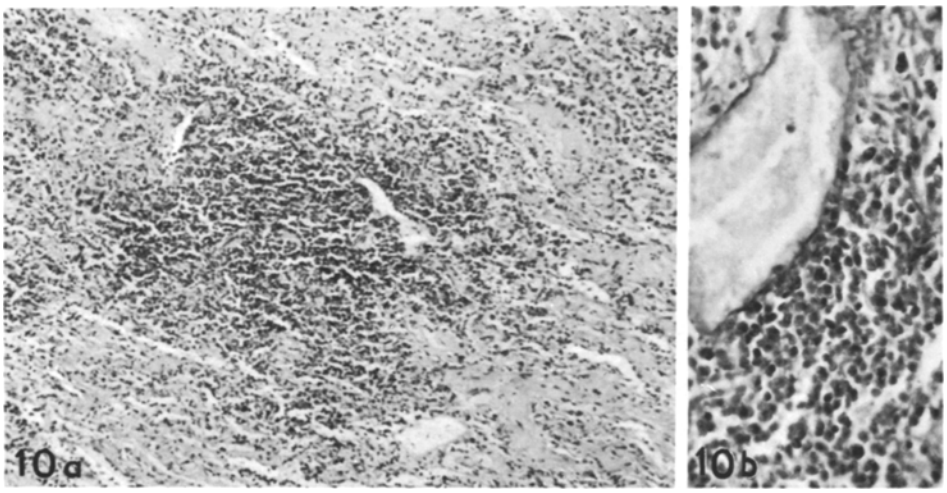

Fig. 10a and b. Case 2. Autopsy material (lung): **a** Angiocentric feature of the infiltrate is shown; the alveolar pattern of the lung tissue is not recognizable (H.E. ×200), **b** Infiltration at the wall of the small venule located at the center (H.E. ×480)

around a necrotic center (Fig. 8). The cells were composed of histiocytes, with prominent nuclear pleomorphism and mitotic figures, lymphocytes, plasma cells and a small proportion of lymphoblasts (Fig. 9). The infiltrates were usually centered by arterioles or venules with signs of invasion and occasionally destruction of the latter. There were no signs of necrotizing vasculitis (Fig. 10).

The remainder of the lung parenchyma showed a dense intraalveolar exudate composed of neutrophils and fibrin. Hyaline membranes were present in large amounts. Pneumocystis carinii were observed on special stains though to a lesser degree than within the biopsy described in the clinical findings. A Gram stain revealed the presence of numerous Gram-negative rods.

The rest of the autopsy revealed no further dissemination of the lesions.

Discussion

Nonhealing granuloma of the nasal cavity was first described by Stewart in 1933. His description was essentially of clinical nature, without pathological criteria, that is chronic necrotizing granulomatous lesions in the upper air passages, nose and mid-face with fatal evolution. In view of the similarity with Wegener's granulomatosis, Friedman et al. (1978) distinguished two forms, i.e., a limited form without vasculitis or Stewart's type, and association of systemic lesions with vasculitis or Wegener's type.

Polymorphic reticulosis, Wegener's granulomatosis and lymphoma of the facial mid-line region have, in the past, been assimilated under the term "lethal midline granuloma" (Allison and Rappaport 1976; Eichel and Mabery 1968; Kassel et al. 1969; McGuirt and Rose 1976). It is thus necessary to establish

a differential diagnosis between these three entities often labelled by this unsatisfactory clinical term.

Wegener's granulomatosis is characterized by vasculitis with necrotizing granulomas, giant cells and histiocytes (Liebow et al. 1972). Both the limited and the disseminated forms present identical morphological findings. Polymorphic reticulosis differs by the absence of vasculitis and distinct giant cell granulomas. When the kidneys are involved in Wegener's disease, the lesion is usually glomerulonephritis, whereas in polymorphic reticulosis there is periglomerular infiltration of cells identical to that found at other sites, involving atypical histiocytes. There is absence of glomerulonephritis (Fauci et al. 1976; Katzenstein et al. 1979; Lee et al. 1975; McDonald et al. 1976; MacKinnon 1970; Michaels and Gregory 1977). Differential diagnosis may nevertheless be challenging, especially when extensive "secondary" vascular destruction or necrosis are present. It is necessary to inspect a large number of arterioles and veins in a tissue sample before excluding Wegener's granulomatosis, as it may be that only a few vessels show the characteristic signs of necrotizing vasculitis in this disorder.

To most pathologists, polymorphic reticulosis has a neoplastic nature as a result of the invasive quality of the cells forming the infiltrates and their frequent immaturity. In contrast to malignant lymphoma with a monomorphic or bimorphic cell population, polymorphic reticulosis has a mixed population of cells, of which many., if not the majority, have a benign character on histological grounds. Malignant lymphoma may show a reactive inflammatory infiltrate, but this is far less extensive than that seen in polymorphic reticulosis (Friedman et al. 1978; Fu and Perzin 1979; Lee et al. 1976; Michaels and Gregory 1977). Differential diagnosis between these two entities may be complicated by the presence in polymorphic reticulosis of a large number of atypical histiocytes or lymphoblasts. It is important to mention that the cellular infiltrates are composed of the same elements as those found in Hodgkin's disease, but that the angiocentricity and destruction as well as absence of Reed-Sternberg cells in polymorphic reticulosis allow a relatively easy distinction between the two diseases (Fu and Perzin 1979; Liebow et al. 1972).

Since its definition as a separate pathologic entity by Liebow et al. in 1972, lymphomatoid granulomatosis has remained a rare disease although several well documented series, including one of 152 cases by Katzenstein et al. (1979), have been reported. In addition to these series, several authors have reported isolated cases of the disease (Anderson et al. 1975; Chen 1977; Damjanov et al. 1975; Gibbs 1977; Kay et al. 1974; Lee et al. 1976; Pena 1977; Saldana et al. 1977; Weisbrodt 1976; Yockey 1977). In the second case described in this paper, pulmonary lesions similar to those initially described by Liebow were found. However, associated with these were lesions of the midfacial region and the skin. Although the skin has been described as a site of lymphomatoid granulomatosis in conjunction with the lungs (DeRemee et al. 1978; Gibbs 1977; Katzenstein et al. 1979; Kay et al. 1974; Lee et al. 1976; Pena 1977), Liebow's definition of the disease excluded midfacial involvement. Despite this fact, the gross findings and the angiodestructive polymorphocellular infiltrates in our cases lead us to believe that we are dealing with the same disease.

Furthermore DeRemee (1978) has described 13 cases out of a series of 40 with associated midfacial and pulmonary lesions.

Eichel and Mabery (1968) studied 33 cases that were initially thought to represent nasal lymphoma. On re-examination of the pathology material, they found 9 patients who had particular polymorphocellular lesions and who had prolonged survival following radiation therapy. The term polymorphic reticulosis was used to describe this lesion which, according to its morphologic description, is the same as that described by Liebow. However, in their initial study, Eichel and Mabery (1968) reported systemic dissemination to distant sites, such as the skin, but there is no mention of associated pulmonary lesions. Kassel et al. (1969) used the term "midline malignant reticulosis" as a synonym for polymorphic reticulosis and believed that midline malignant reticulosis should be placed in the category of lymphosarcoma. In this review, it was noted that the disease process could be either localized to the facial area or disseminated to the lungs, skin and other organs. Thus, on the basis of different anatomical localizations, two different names were given to a disease process with apparently the same morphological characteristics. On the basis of the findings in our second case and reports of other authors who have found pulmonary and co-existing midfacial involvement, we believe that these two entities probably represent the same disorder (Crissman 1979; DeRemee et al. 1978; Fu and Perzin 1979; Katzenstein et al. 1979; Lee et al. 1976; McDonald et al. 1976).

It is important to differentiate between localized and disseminated forms of polymorphic reticulosis, especially in view of therapeutic considerations. It has been reported in several clinical studies that the localized forms respond more favourably to radiation therapy, whereas chaemotherapy has a better effect on the disseminated forms (Allison and Rappaport 1976; Fu and Perzin 1979; Katzenstein et al. 1979; McDonald et al. 1976).

If morphological characteristics allow a separate classification of this disease, its pathogenesis is as yet unknown. Is it truly a separate disease process? Is it in some way related to Wegener's granulomatosis, or is it a lymphoma which occupies a so-far undetermined locus in the spectrum of lymphoproliferative disorders? Furthermore what relation is there, if any, between Hodgkin's disease and polymorphic reticulosis, since the granulomatous character is a common denominator of both diseases? Further studies are necessary to elucidate these unanswered questions.

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References

Allison GR, Rappaport I (1976) Lethal midline granuloma. Plast Reconstr Surg 58:434–439

Anderson JM, Jamieson DG, Jefferson JM (1975) Non-healing granuloma and the nervous system. Q J Med 174:309–323

Chen KTK (1977) Abdominal form of lymphomatoid granulomatosis. Hum Pathol 8:99–103

Crissman JD (1979) Midline malignant reticulosis and lymphomatoid granulomatosis. Arch Pathol Lab Med 103:561–564

Damjanov I, Durakovic Z, Radonic M (1975) Lymphomatoid granulomatosis of the lung associated with active tuberculosis. Z Erkr Atmungsorgane 143:56–60

DeRemee RA, Weiland LH, McDonald TJ (1978) Polymorphic reticulosis, lymphomatoid granulomatosis. Two diseases or one? Mayo Clin Proc 53:634–640

Douglas AC, Anderson TJ, MacDonald M (1976) Midline and Wegener's granulomatosis. Ann NY Acad Sci 278:618–635

Eichel BS, Mabery TE (1968) The enigma of the lethal midline granuloma. Laryngoscope 78:1367–1386

Fauci AS, Johnson RE, Wolff SM (1978) Midline granuloma or Wegener's granulomatosis. Ann Intern Med 84:609–610

Friedman I, Sando I, Balkany T (1978) Idiopathic pleomorphic midfacial granuloma (Stewart's type). J Laryngol Otol 92:601–611

Fu YS, Perzin KH (1979) Nonepithelial tumors of the nasal cavity, paranasal sinuses and nasopharynx. A clinicopathologic study. X. Malignant lymphomas. Cancer 43:611–621

Gibbs AR (1977) Lymphomatoid granulomatosis – a condition with affinities to Wegener's granulomatosis and lymphoma. Thorax 32:71–79

Kassel SH, Echevarria RA, Guzzo FP (1969) Midline malignant reticulosis (so-called lethal midline granuloma). Cancer 23:920–935

Katzenstein ALA, Carrington CB, Liebow AA (1979) Lymphomatoid granulomatosis. A clinicopathologic study of 152 cases. Cancer 43:360–373

Kay S, Fu YS, Minars N, Brady JW (1974) Lymphomatoid granulomatosis of the skin: light microscopic and ultrastructural studies. Cancer 34:1675–1682

Lee SC, Roth LM, Brashear RE (1976) Lymphomatoid granulomatosis. A clinicopathologic study of four cases. Cancer 38:846–853

Liebow AA, Carrington CRB, Friedman PJ (1972) Lymphomatoid granulomatosis. Hum Pathol 3:457–558

Liebow AA (1973) Pulmonary angiitis and granulomatosis. Am Rev Respir Dis 108:1–18

McDonald TJ, DeRemee RA, Harrison EG Jr, Facer GW, Devine KO (1976) The protean clinical features of polymorphic reticulosis (lethal midline granuloma). Laryngoscope 86:936–945

McGuirt WF, Rose EF (1976) Lethal midline granuloma: a pathological spectrum. J Laryngol Otol 90:459–466

MacKinnon DM (1970) Lethal midline granuloma of the face and larynx. J Laryngol Otol 84:1193–1203

Michaels L, Gregory MM (1977) Pathology of "non-healing (midline) granuloma". J Clin Pathol 30:317–327

Pena CE (1977) Lymphomatoid granulomatosis with central involvement. Light and electron microscopic study of a case. Acta Neuropathol 37:193–197

Saldana MJ, Patchefsky AS, Israel HI, Atkinson GW (1977) Pulmonary angiitis and granulomatosis. The relationship between histological features, organ involvement, and response to treatment. Hum Pathol 8:391–409

Stewart JP (1933) Progressive lethal granulomatous ulceration of the nose. J Laryngol 48:657–701

Weisbrodt IM (1976) Lymphomatoid granulomatosis of the lung, associated with a long history of benign lymphoepithelial lesions of the salivary glands and lymphoid interstitial pneumonitis. Report of a case. Am J Clin Pathol 66:792–801

Yockey CC (1977) Lymphomatoid granulomatosis presenting as a fever of unknown origin. JAMA 237:2633–2634

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