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Leukaemoid Reaction and Eosinophilia in "Inflammatory Fibrous Histiocytoma"

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Summary. A case of retroperitoneal inflammatory fibrous histiocytoma associated to a marked granulocytic blood reaction and high eosinophilic count is reported. The paraneoplastic nature of the haematological findings and their probable prognostic role are discussed. Ultrastructurally the tumor does not differ significantly from "non inflammatory" fibroxanthosarcomas.

Key words: Sarcoma – Histiocytic – Leukaemoid reaction.

Introduction

In 1964 O'Brien and Stout described the sarcomatous variants of benign fibrohistiocytic neoplasms commonly arising from the skin. Microscopically the malignant fibrous histiocytomas showed fibroblastic storiform patterns and/or histiocytic, often xanthomatous, giant cell components. The criteria for malignancy were based mainly on the infiltrative nature of the growth and the mitotic rate, and the presence of metastasis.

Kempson ane Kyriakos (1972) introduced the term of fibroxanthosarcoma to designate similar growths. These authors (1976) also identified seven cases of a special subgroup of fibroxanthosarcomas characterized by a variegated histology in which histiocytoid and storiform patterns predominated. The hallmark of the lession was the rather dense inflammatory cell infiltrate permeating the tumor. The term "Inflammatory Fibrous Histiocytoma" (Kyriakos and Kempson 1976) synthesizes the microscopic morphology of the growth. Over 50% of these neoplasias are associated with elevated white cell counts in the peripheral blood (Kyriakos et al. 1976). Recently, Roques, Horton, Leslie and Buxton-Thomas (1979) added a case associated with a leukaemoid reaction.

A further case of Inflammatory Fibrous Histiocytoma associated with an elevated white cell count and marked eosinophilia is reported here.

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Case Report

Three weeks before admission, this 71-year-old-female complained of left upper quadrant abdominal pain. Roentgenograms disclosed a large left upper retroperitoneal mass displacing the stomach anteriorly and to the right. Laboratory data on admission included a haemoglobin of 10.7 gm%, haematocrit 36%, red cell count 4.2×10^6, platelet count 450,000 and a white cell count of 24,000 with 37 eosinophils and 54 neutrophils. Many of the neutrophils showed Döhle bodies and toxic granulation. An urinalysis was negative. Three blood cultures were negative. An SMA profile only showed a discrete hypoproteinemia and hypocalcemia. An alpha fetoprotein was negative. She was apyrexial. On the fourth hospital day, she underwent an exploratory laparotomy and a biopsy was taken from the mass. The frozen section diagnosis was fibrosarcoma. Following initial sectioning of the biopsy material, portions of the tumor were placed in 3% glutaraldehyde and processed for electron microscopy. A postoperative blood count revealed 43,000 leukocytes with 30 neutrophils, 35 bands, 5 metamielocytes and 22 eosinophils. A bone marrow aspiration disclosed granulocytic hyperplasia and depressed erythropoiesis. She run a down-hill course with low grade fever and died on the seventh postoperative day. A complete autopsy was performed. The tumor was in the left retroperitoneal space, above the kidney and partially adherent to spleen and larger gastric curvature. It was rounded, soft, centrally necrotic and measured 10 cm in diameter. No metastatic foci were found anywhere. The liver and spleen were normal in size and showed no significant findings microscopically.

Results

Although the tumor appeared well delineated on gross examination, microscopically it infiltrated retroperitoneal fat. The two histological patterns, *fibroblastic-storiform* and *histiocytic* (Fig. 1) were equally represented. Abundant reticulin and collagen were demonstrated in the fibroblastic areas with the Gomori and Trichrome special stains. *Giant-cells* of the type shown in Fig. 1 were easily identified in the histiocytic fields, but xanthomatous *Touton type* giant cells were not observed. The Oil-red-0 special stain was negative. Overall the cellular appearance was bland and mitosis were not common. Other malignant features such as cellular and nuclear pleomorphism and hyperchromatism were minimal. The most interesting finding was the massive *inflammatory cell infiltrate* that permeated viable non-necrotic areas of the tumor (Fig. 2). The infiltrate was diffuse but of variable degree. It was largerly composed of neutrophils with a considerable number of eosinophils and a few scattered plasma cells, mast cells and lymphocytes. Megakariocytes could not be demonstrated.

Electron Microscopy. The tumor cells in the histiocytic portions displayed polymorphic shapes with interdigitating densely packed, finger-like cytoplasmatic projections (Fig. 3). The nuclei were enlarged, lobulated, deeply indented and often contained one spheroidal body (Fig. 4). The nucleoli were prominent. The cytoplasm included well developed Golgi, lysosomes, small mitochondria and discrete amounts of lipid vacuoles. Xanthomatous lipid-laden cells were not found. Solitary cisternae of RER were scattered through the cytoplasm. Delicate filaments, occasionally grouped in bundles, were more prominent within the cytoplasmatic processes. Desmosome-like junctions, centrioles and cilia were seen in a few cells. Neutrophils infiltrated the intercellular spaces densely throughout the tumor and were also occasionally demonstrated within the cytoplasm (Fig. 5).

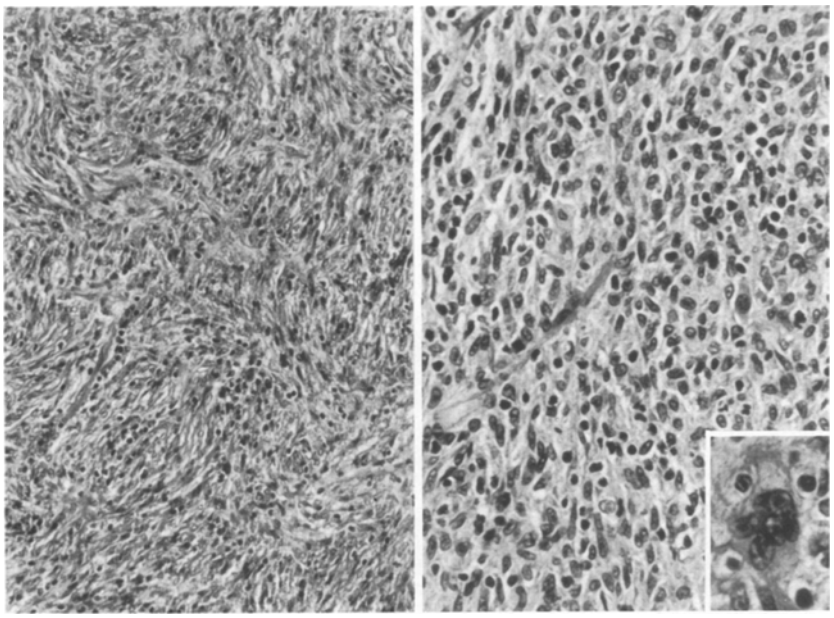

Fig. 1. (*Left*) Tumor area showing a fibroblastic storiform pattern and displaying an inflammatory, mostly neutrophilic, infiltrate. H & E ×100. (*Right*) Tumor area with an histiocytic appearance, also heavily infiltrated by inflammatory cells. H & E ×200. (*Inset*) Histiocytic multinucleated tumor giant cell. H & E ×400

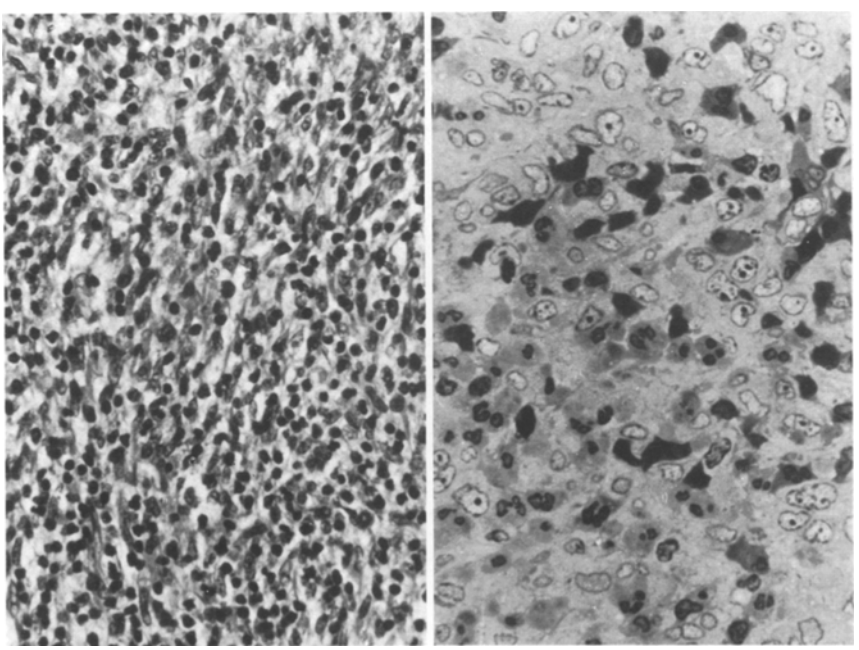

Fig. 2. (*Left*) High density inflammatory cellular infiltration overshadowing the tumor cells. H & E ×200. (*Right*) Resin embedded semi-thin section showing neutrophils permeating the intercellular spaces. Toluidin blue ×500

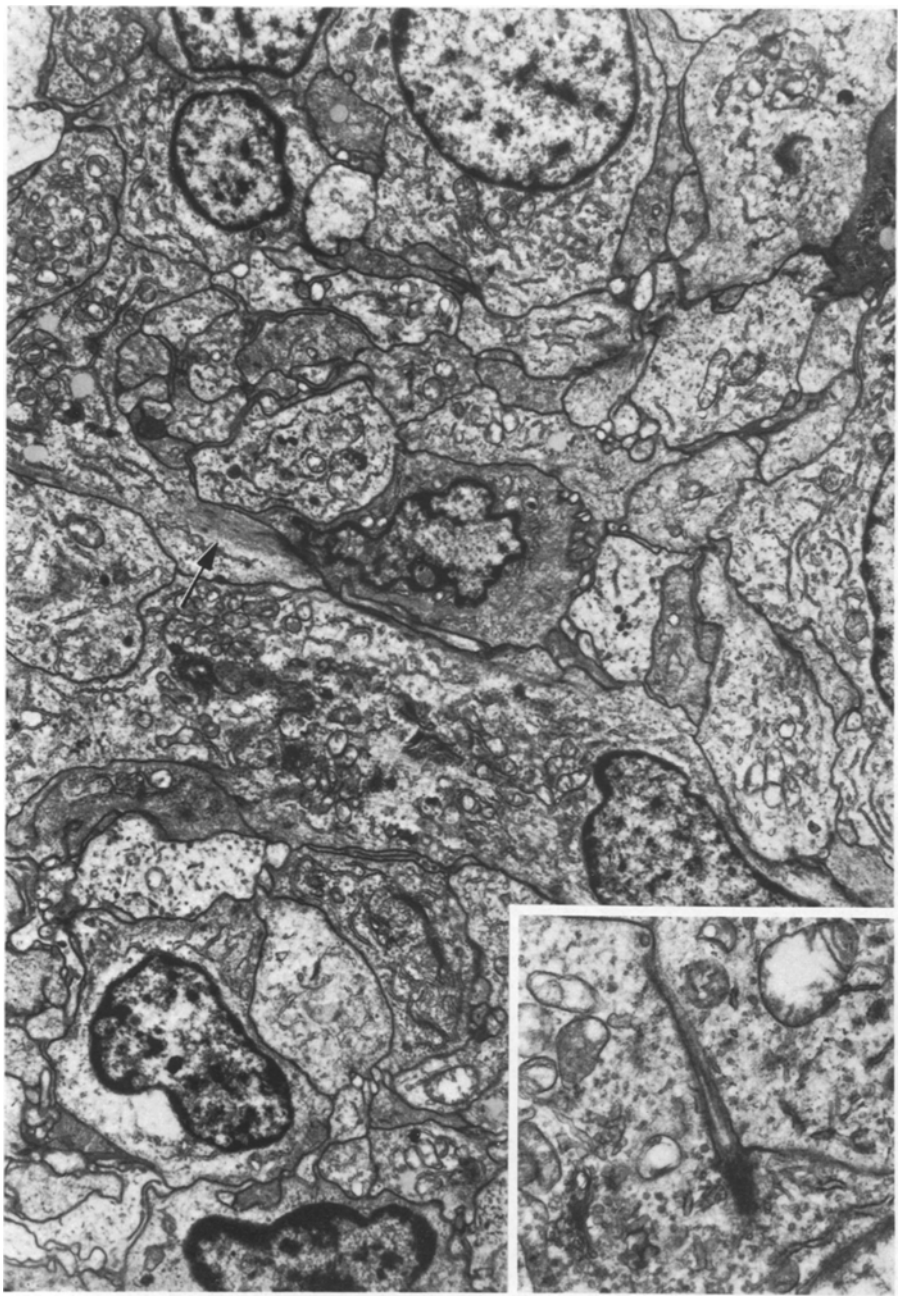

Fig. 3. Histiocytic tumor cells with interdigitating cytoplasmic processes. Microfibrillary aggregates can be seen within the cellular expansions (*arrow*). Electron micrograph ×7,800. (*Inset*) Well developed extracellular cilium in a tumor cell. ×19,800

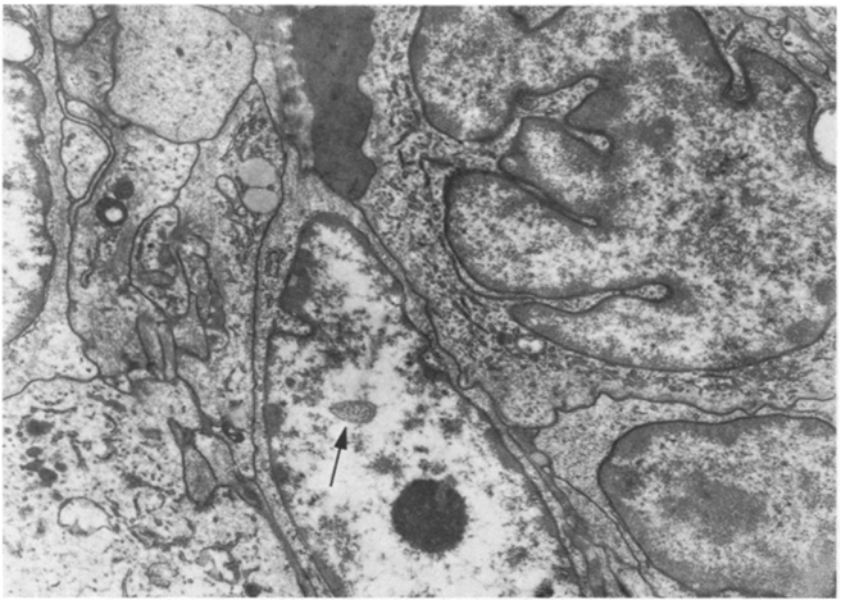

Fig. 4. Tumor histiocytic cells. Deep nuclear indentations and intranuclear spheroidal body (*arrow*). Electron micrograph. × 15,000

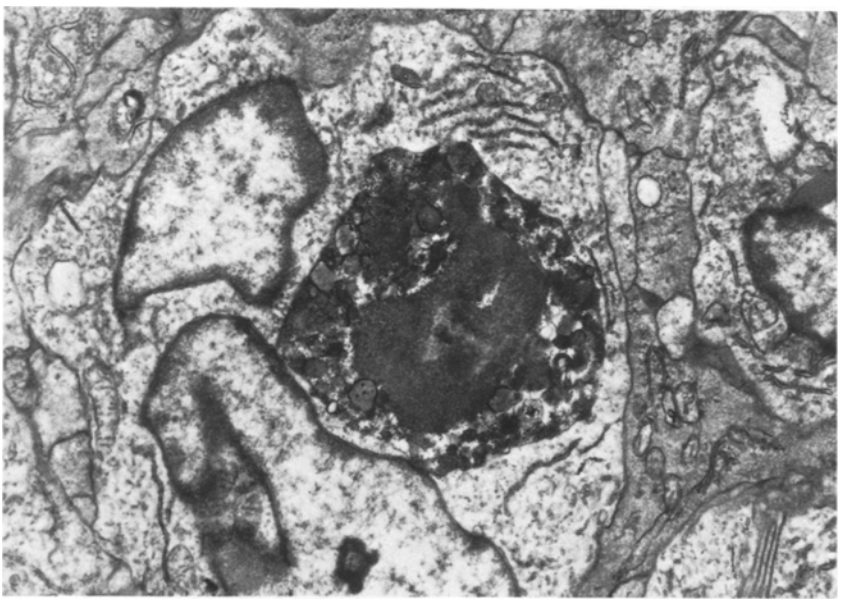

Fig. 5. Electron micrograph showing a tumor histiocyte containing a partially digested intracytoplasmatic polymorphonuclear leukocyte. × 15,000

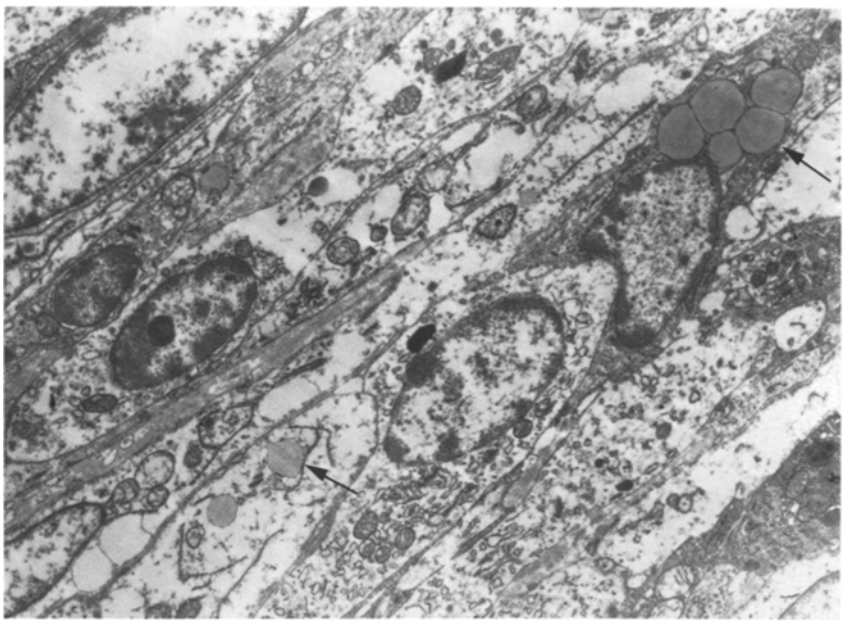

Fig. 6. Spindle-shaped tumor cells from fibroblastic areas. Lipid droplets (*arrow*) are also present. Electron microph. ×9,900

The storiform component of the tumor consisted of spindle shaped cells with smooth outlines, elongated nuclei and non remarkable cytoplasm (Fig. 6). Collagen was easily identified in the intercellular spaces.

Discussion

In addition to the storiform and histiocytic-multinucleate components, all the reported cases (Kyriakos et al. 1976; Roques et al. 1979) described groups of foamy histiocytes and/or positive Oil-red-0 staining. The present case showed only some vacuolated histiocytes and Oil-red-0 performed on formaldehyde fixed tissue was negative. Electron microscopy disclosed only occasional cytoplasmic lipid vacuoles. Apart from the inflammatory component, the ultrastructural findings were similar to those previously reported in fibroxanthosarcoma (Merkow et al. 1971).

Tumor necrosis considered to be uncommon in this entity (Kyriakos et al. 1976) was a prominent feature here, particularly in the necropsy material. Although the role of necrosis in the granulocytic response remains unclear, the massive neutrophilic infiltrate present in areas of viable tumor away from the necrotic foci, tends to rule out the necrosis as a important chaemotactic factor. The ultrastructural observations reinforce the viable nature of the tumor cells which are heavily infiltrated by the inflammatory cells. The marked eosinophilia is an added new feature of the granulocytic reaction not previously reported.

We believe that the more specific nature of eosinophilic responses adds strength to the hypothesis suggested by Roques et al. (1979) which proposed that the leukocytic reaction is secondary to a granulopoietic factor secreted by the tumor. Granulopoietic factors have been demonstrated in mice with leukaemoid reactions secondary to transplanted tumors (Delmonte et al. 1966; Kodama, Sendo and Kobayashi 1974). The granulocytic hyperplasia and the elevated eosinophil count, demonstrated in the marrow aspirate, also supports this view. So far all the evidence points to a new paraneoplastic syndrome associated with this peculiar variant of fibroxanthosarcoma.

With regard to *prognosis* Kyriakos et al. (1976) point out the generally rapid fatal course of these neoplasms, with an average survival from the time of initial diagnosis of 53 months. It is significant that the survival time is considerably shortened in those patients with granulocytic blood reactions. The case reported by Roques et al. (1979) and the present case appear to confirm the particularly rapid outcome.

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