MALIGNANT SYNOVIOMA

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Tumors of the synovial tissues are rare. The following report of a fatal synovial neoplasm originating from the medial aspect of the knee (bursa anserina) illustrates the difficulties of diagnosis and treatment, while a study of the primary growth and the lung metastasis throws some light on the nature of these tumors and on the structure of the normal synovial membrane from which they originate.

CASE REPORT

Mrs. C., aged twenty-eight years, was first seen in June 1931, complaining of a swelling below the left knee, which had appeared two years previously following trauma. Examination revealed a tender fluctuant mass at the upper and inner end of the tibia, and a diagnosis of bursitis was made. The swelling failed to respond to rest, however, and continued to increase in size. In August 1931 a cystic mass was removed which extended from the medial aspect of the knee toward the popliteal space. The pathological report was made by Drs. Brem and Zeiler.

The specimen contained a cyst about 10 cm. long and 4 cm. wide. The cyst lining was smooth, but in the walls was a thickened cellular yellow tissue. Three free masses of soft cellular tissue were also present, having the same appearance. Microscopic sections (Fig. 1) showed irregular gland-like structures, lined with one to several layers of cells resembling epithelium, with occasional mitotic figures. The lumina contained a hyaline material. In the stroma were some large pigmented cells, probably phagocytes. The diagnosis was embryonal adenomyosarcoma of low-grade malignancy.

Amputation was advised but refused, and deep roentgen therapy was given (Dr. Warren), totalling 2800 r. No invasion or metastasis could be demonstrated roentgenographically.

Following her discharge the patient resumed her normal activities, reporting for examination from time to time. In June 1933 a small nodule was discovered in the scar over the knee. This was removed under local anesthesia on July 10. The pathological diagnosis was spindle-cell sarcoma. Amputation was again declined, and another course of irradiation was given.

Some time later the diameter of the leg below the knee began to increase and a tumor appeared in the soft tissues. In December 1934 the patient was seen by the Malignancy Committee of the Hollywood Hospital. Examination showed a fixed, hard, irregular, pear-shaped swelling, beginning at approximately the upper inner aspect of the left tibia. There was still no roentgen evidence of bone involvement or lung metastasis, nor were there palpable nodes in the groins or popliteal spaces. Roentgen therapy was given, 6300 r between Dec. 4, 1934, and Jan. 12, 1935. By the middle of March the tumor had almost disappeared. In May, however, the circumference of the leg again began to increase and there was some stiffness.

The patient was next seen in December 1935, when examination in the region of the inner aspect of the left tibia revealed a recurrence of the tumor, which seemed now to be as large as or slightly larger than a year earlier. There were no palpable nodes in the groin. Mid-thigh amputation was advised but was again refused.

Sections of the material obtained in 1931 and 1933 were now diagnosed by Dr. Frank

1 Case report by Charles W. Hutchison. Discussion by David H. Kling.
Adair and Dr. James Ewing of the Memorial Hospital, New York, as "malignant synovioma, radioresistant."

Roentgenograms taken on March 2, 1936, revealed a soft tissue tumor in the left knee joint but with no demonstrable evidence of bone pathology (Fig. 2). In the chest were large nodules in the upper and outer portion of the left upper lobe. There was also evidence of a pleurisy with effusion at the base of the left lung. A diagnosis of pulmonary metastasis and pleurisy was made.

The patient refused further medical advice and was not seen again until June 1936. She had now lost considerable weight. The tumor over the left knee had increased only slightly in size. It did not interfere seriously with motion and was not very painful or tender on palpation. There was still no involvement of the lymph nodes of the groin. The left chest, however, was almost entirely dull to percussion and roentgenograms showed a homogeneous shadow over the left lung. The heart was pushed to the right of the median line. The patient grew gradually weaker and began to have difficulty in swallowing and in breathing. Death occurred on Aug. 18, 1936.

**Fig. 1.** Primary Malignant Synovioma of the Bursa Anserina, Showing Sarcomatous Areas Containing Densely Packaged Spindle Cells and Gland-like Areas Lining Cavities Containing Precipitated Fluid. $\times 300$

Autopsy, performed by Dr. Andrews, pathologist of the Hollywood Hospital, showed a tumor of the inner aspect of the knee which was quite firm. Dissection of the tumor was not permitted.

The left pleural cavity was filled with tumor and contained considerable blood-stained, mucinous fluid, having the character of synovial fluid. The heart and mediastinum were pushed to the right, the heart extending over to the mid-axillary line compressing the right lung. The left lung was not visible and in attempting to remove the tumor various small cystic cavities were entered. Each of these contained tumor growths, which shelled out as though they were without attachment; some of these were quite large. The cavities measured 10 to 12 cm. in diameter and were filled with fluid and masses of 6 to 7 cm. in diameter. The lung was pushed upward and covered with this growth, but there was little involvement of the lung tissue. The apex of the pleural cavity was prominent, being pushed up into the neck so that vessels in the upper mediastinum were greatly compressed. The right lung was firm, showing some congestion, some atelectasis in the lower lobe, and a small tumor nodule in the anterior border of the right lower lobe. The abdominal findings were not significant.
Diagnosis: Malignant synovioma of the left knee with metastases in the left pleura and lung.

Discussion

Knox in 1936 in a careful survey of the literature recognized 22 cases of synovial sarcoma, including 3 of her own observation. Berger in 1938 eliminated a number of the reported cases because their origin from synovial tissue was not established. He recognized only 23 examples presenting specific synovial features including 4 of his own. He failed, however, to mention Coley and Pierson's report in 1937 of 15 cases of malignant synovial tumors. These authors accepted 20 case reports from the literature as genuine.

The synovial membrane is generally considered as a modified connective tissue, malignant tumors of which should be sarcomas; yet these tumors show a variety of cell-types and arrangements. Besides solid areas there are clefts and cystic spaces filled with a viscid fluid and lined with large polygonal cells often with a glandular arrangement.

Our original tumor, removed in 1931, shows solid parts consisting mostly of spindle cells (Fig. 1). The stroma is either dense or reticular. In other parts are numerous papillae lining irregular clefts of large and small size. The lining cells are polygonal, columnar, and cuboid. The cytoplasm forms a meshwork which is faintly basophilic. The nuclei are round or oval and have a heavy membrane, granular chromatin, and one or two nucleoli. Some cells show mitotic figures and others direct division. The lining cells form a closed epithelioid arrangement but they are not separated by a basal membrane from the stroma. The lumen contains a homogeneous mass taking a reddish stain. On account of the absence of collagen fibers the tissue was originally interpreted as smooth muscle and a diagnosis of embryonic adenomyosarcoma was made. The original tumor is moderately vascular. In places extracellular brownish pigment is present as a result of an extravasation and the stroma contains macrophages loaded with hemosiderin. Areas of transition between the nests of spindle cells and the polygonal cells are seen.

Sections of the tissue removed from the local recurrence two years later showed such a prevalence of solid areas and spindle cells that a diagnosis of spindle-cell sarcoma was made. Sabrazès also described a "typical endothelial (or pseudo-epithelial) synovial sarcoma" with a recurrence suggesting a common fibrosarcoma.

The lung metastases (Figs. 3 and 4) are composed of three distinct elements. First, there are the larger and smaller solid vascular nodes resembling fibrosarcoma, consisting chiefly of spindle cells with oval nuclei. Mitotic figures and direct division are observed in some cells. The blood vessel walls are formed by a layer of endothelial cells. Secondly there are cystic areas filled with a viscid, mucoid fluid. The lining cells, which are large and polygonal, show a gland-like arrangement and form several layers. The cytoplasm is only faintly basophilic. The eccentric nucleus shows a heavier stained rim and a reticular arrangement of the chromatin. These areas correspond to the lining of villi of normal synovial membrane or to hypertrophic chronic synovitis. Finally, there are areas which contain in a loose edematous stroma a variety of cells, such as fibroblasts, stellate cells, and large polygonal
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In the stroma histiocytes can be identified, by phagocytosis of blood pigment and reticulum, with Laidlaw’s silver stain.

This polymorphism of the synovial tumor was described by Lejars and Rubens-Duval in 1910 and has been confirmed by others. It has also been noted in the various reports that the cystic areas contain a fluid and that lung metastases produce an exudative pleurisy. The pleural effusion is usually designated as a serous or serosanguineous exudate. In our case the fluid was found to be viscid and to contain mucin characteristic of synovial fluid.

FIG. 2. ROENTGENOGRAM OF RECURRENT SYNOVIAL TUMOR IN LEFT KNEE-JOINT, ANTERIOR-POSTERIOR VIEW, MARCH 2, 1936, FIVE MONTHS BEFORE DEATH

A soft tissue tumor is visible at the medial aspect, reaching from two inches above to six inches below the knee. Note that the joint cavity, the femur, and tibia are intact.

The explanation of the complex nature of synovial tumors appears to rest upon a consideration of the structure of the normal synovial membrane. Kling has repeatedly pointed out that the current conception of the synovial membrane as a modified connective tissue is no longer tenable. On the basis of his earlier studies and those of Mayeda and Vaubel the hypothesis is advanced that the synovial membrane has a dual structure and function. It consists of a supporting connective tissue in which are interspersed pluripotent and more primitive mesenchymal cells, the chief function of which is the production
of mucin, the component of normal synovial fluid providing for the necessary lubrication of the joint surfaces. Under physiological or pathological stimuli these mesenchymal cells develop endothelial or epithelioid potencies and line cavities which simulate glandular and papillary structures. They never, however, attain the orderly architecture of glands and are not separated from the stroma by a basal membrane. That this polymorphism is not produced by external mechanical factors such as pressure and stress of articular functions, assumed by many authors (Key), was demonstrated by Vaubel, who found the same polymorphism in tissue cultures of the synovial membrane of rabbits. By Kling's precipitation phenomena (sac and tube reaction) Vaubel was able to show that mucin was present only as long as the tissue cultures were healthy. This is important evidence against the widespread assumption that mucin is a product of desquamation of either synovial lining cells or of cartilage cells, an assumption which has also been refuted by chemical studies (Kling).

Malignant change in the supporting connective tissue results in the formation of sarcomatous areas; in the synovial lining cells it results in the cystic areas with clefts and gland-like arrangements. Where both elements are intermingled a composite picture results. Mitosis and direct division can be seen in cells of both types, indicating that both are actively participating in the composition of the tumor. The pleural effusion in our case, as pointed out, had the characteristics of synovial fluid, indicating that the synovial cells continue to elaborate mucin even after transplantation to a distant part of the body. This persistence of the characteristics of synovial tissue within the metastasis adds further support to the conception of the dual nature and function of normal synovial membrane.

Franceschini regards the characteristic areas of the synovial membrane as a reticulo-histiocytic meshwork. In this he is supported by Sabrazé and his coworkers who, with Berger, consider the malignant tumors of the synovial membrane chiefly as reticulo-histiocytosarcomas. Berger finds evidence for this conception in the rich network of reticular fibrils demonstrated by Laidlaw's silver stain in some areas of his synovial tumors, and in the presence of macrophages, lipopexic and giant cells which give rise to xanthomas and giant-cell tumors of the synovial membrane.

This classification of the synovial membrane in the reticulo-endothelial system and the extension of the many functions of this system to include mucogenesis do not offer an adequate interpretation of the structure of normal or pathological synovial membrane. Berger himself recognizes this when he points out that “in spite of this kinship the synovial tissue has some peculiar characters setting it apart as a variety sui generis of the reticulo-histiocytic system as a whole. These features are, above all, the frequency and the intensity of the endothelial aspect and the appearance of true mucin.”

The characteristic element of the synovial membrane, the mucogenous synovial cell, is devoid of the elementary function of the histiocyte, phagocytosis. After intravenous or intra-articular injection of colloidal dyes such as trypan blue, the histiocytes in the synovial membrane are found to be packed with coarse granules but the synovial cells store none or only very fine granules. Berger accepts Vaubel's conception of the synovial cell as an autonomous type resembling but differing from the osteoblast and chondroblast and therefore
Fig. 3 (above) shows an area of fibrosarcoma (× 700); Fig. 4 (below) the gland-like arrangement of the synovial cells in several rows lining a cystic area (× 300).

designated as a "synovioblast," its chief function being the formation of synovial fluid and synovial mucin analogous to the intercellular substance of cartilage or bone. If we follow Berger's conception, not only the synovial membrane, but also cartilage and bone would have to be accepted as reticuloendothelium.
It is true that most of the mucin stains fail to demonstrate intracellular mucin and that synovial mucogenesis is different from that of mucous glands. That it is the product of healthy cells, however, has been demonstrated beyond doubt by tissue cultures (Vaubel). Kling has previously pointed out that synovial fluid conforms more closely to the recognized morphological and physiological criteria of a secretion than of an interstitial matrix. Our conception of the dual nature of the synovial membrane appears to be a simpler and perhaps more adequate explanation of the structure of the normal synovial tissue and of synovial tumors.

**Summary**

A case of malignant synovioma arising from a bursa at the medial aspect of the knee joint is described. Repeated excision and x-ray treatments failed to prevent local recurrences and lung metastasis. Death occurred seven years after the first symptoms. The primary tumor, as well as the metastasis showed the complex structure typical of synovial tumors, consisting partly of solid masses and partly of cystic and cleft-like spaces lined by papillomatous growths of glandular structure, containing one or several rows of large polygonal cells. The lumen contained a viscid, mucous, synovial-like fluid. This complex structure is explained on the basis of a dual structure and function of normal synovial membrane (Kling).

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