

PRIMARY SPLENIC SARCOMAS OF HODGKIN'S TYPE

Review of the Literature and Report of 2 Cases

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PRIMARY malignant disease of the spleen remains a rare entity despite improvements of diagnosis and more voluminous reporting in the literature with the passing of years. Hausmann and Gaarde¹ reviewed the literature to 1940 and found a total of 178 cases, 9 of which they added from the Mayo Clinic. Twenty of these cases, however, were unconfirmed, the reports being indexed but the journals unavailable.

From 1940 to 1945, 10 more cases appear in the literature. Two of these, 1 a primary sarcoma² and the other a malignant hemangio-endothelioma also involving the liver,³ are reported in unavailable journals. Garlock⁴ reported an angiosarcoma; Goldberg,⁵ a malignant solitary hemangioma cavernosum, a solitary macrocystic lymphangioma, and a multiple macrocystic lymphangioma; Siirala and Nääätänen,⁶ a primary malignant hemangioma with metastasis to the liver; Brule, Hillemand, and Isch-Wall,⁷ successful splenectomy for lymphoma of the spleen with uneventful four-year follow-up; Bonney,⁸ a lymphosarcoma; and Tomlinson,⁹ a primary microcystic lymphangioma.

We report 2 sarcomas of the spleen from Cleveland Clinic, bringing the total of reported cases of all types of primary splenic malignant disease to 190. These 2 cases constitute the only primary malignant tumors of the spleen seen at Cleveland Clinic in two decades. In 20,000 major surgical procedures, only 1 splenectomy for primary splenic malignant disease has been performed, as indicated in the second case report.

Case Reports

Case 1. A white man, aged 50, was seen in consultation with Dr. Perry King, Alliance, Ohio, with a history of persistent generalized lower abdominal pain of ten months' duration, unrelieved at the time of its onset by a right herniorrhaphy. Surgical exploration of the gall-bladder and appendix had been made four months later following x-ray examinations. Still unrelieved, the patient had been examined again by x-ray the latter part of January, 1937, at which time a lesion in the colon was suspected. He gave the history of a great deal of weight loss but no intestinal symptoms.

Examination revealed a large, firmly fixed mass in the left upper quadrant, giving the impression of carcinoma beginning in the tail of the pancreas, or possibly of hypernephroma of the left kidney. Both conditions were inoperable at this stage. The patient died on July 25, 1937, the left upper abdominal mass never having become more clearly defined than at the time the patient was first seen at the Clinic in February.

Autopsy revealed a large, indurated, nodular pancreas and surrounding lymph nodes.

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The pancreas weighed 185 Gm.; the left half was involved by a diffuse tumor growth consisting of fairly firm, white, cellular tissue which cut with considerable resistance.

The spleen was enlarged, weighing 385 Gm., and was irregular, with several large masses protruding from the outer surface. On section the tumor nodules were seen to be well localized, irregularly distributed, and varied from 2 to 5 cm. in diameter. They consisted of firm, homogeneous, white tissue with considerable stroma. The left kidney weighed 190 Gm. and measured $10 \times 5.5 \times 5$ cm. The kidney was deformed from the pressure of the splenic tumor. Longitudinal section through the kidney showed dilatation of the pelvis and calices. No calculi nor tumor nodules were present. A portion of adrenal gland which had been compressed by the tumor was attached in the fatty tissue to the upper pole of the kidney. The prosector described no involvement of abdominal lymph nodes other than those adjacent to the nodular portion of the pancreas.

Histologic examination of the spleen showed a sarcomatous growth apparently originating in the reticular or connective tissue of the spleen. The growth was exceedingly cellular, the cells varying enormously in size, shape, and nuclear content. Many mononucleated and multinucleated giant cells were present (fig. 1). Sections from the left half of the pancreas and adjacent lymph nodes showed a tumor similar to that in the spleen. Sections from the

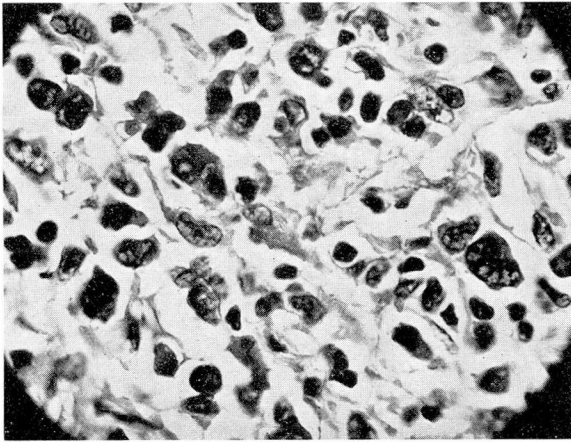


FIG. 1. Case 1. Microscopic section of spleen showing Sternberg-Reed giant cells (x850).

right portion of the pancreas and from the left kidney and adrenal gland showed no neoplasm. The diagnosis was sarcoma of the spleen with secondary involvement of the pancreas. Because of the Sternberg-Reed giant cells and the presence of connective tissue proliferation the tumor is now believed to be a Hodgkin's type of sarcoma. The histologic examination, together with the absence of involvement of any lymph nodes discoverable in the body except those immediately surrounding the portion of the pancreas involved by tumor, indicated that the neoplasm arose in the spleen.

Case 2. A woman, aged 64, was first seen on January 21, 1946, complaining of "sickening" pain in the left lower quadrant of two years' duration. For several months she had noticed increasing constipation and occasional bloody stools. Indigestion, nausea, and vomiting had been mild until three weeks prior to admission, when she began vomiting after almost every meal, sustaining sharp pain in the left side of the abdomen with each bowel movement and with micturition. X-ray films taken previously appeared to demonstrate neoplasm of the splenic flexure of the colon, although the previous fluoroscopic report states that an organic lesion of the sigmoid was suspected. The patient had lost 70 pounds in the past two years.

Physical examination revealed a rough, blowing systolic mitral murmur. Many small diffuse masses were present in each breast. An elongated mass adherent to surrounding deep tissues was felt in the left upper quadrant of the abdomen. A hard, tender mass, the size of

a baseball and not readily movable, could be palpated in this same region. Proctoscopic examination was negative for 25 cm.; x-ray examination of the chest negative; red blood cell count 5,040,000; hemoglobin, 13 Gm.; white blood cell count 14,250; 64 per cent neutrophils, 22 per cent lymphocytes, 3 per cent eosinophils, 9 per cent monocytes. Platelets and hemorrhagic studies, normal; investigation of blood chemistry, normal; Kahn and Wassermann tests, negative.

The preoperative diagnosis was neoplasm of the splenic flexure of the colon. At operation on January 30, 1946, the colon appeared normal, and no metastases were found in the liver. The spleen appeared about four times its normal size, with a rounded, elevated tumor mass involving the lower third and erasing the splenic notch. The top of this tumor had been mistaken for a baseball-sized mass in the colon. There were several enlarged pecan-sized lymph nodes at the hilus of the spleen. The spleen and several adjacent lymph nodes in the region of the splenic pedicle were removed. Nodules apparently involved by the neoplasm remained in the area of the pedicle and could not all be removed, but no retroperitoneal lymph node tumors were palpated. The gallbladder contained one stone the size of a plum.

There was no significant change in the blood picture following operation. A sternal puncture showed neither evidence of leukemia nor any malignancy. The patient had an uneventful recovery except for slight temperature elevation and mild nausea. The spleen weighed 806 Gm., measuring 22.8 x 12.3 x 8.7 cm. It was irregular in shape, nodular (fig. 2),

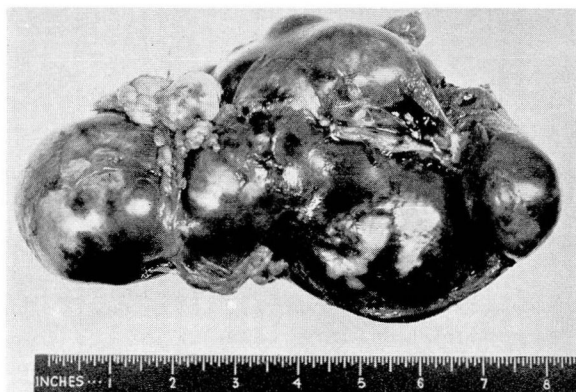


FIG. 2. Case 2. Gross specimen of spleen.

and numerous enlarged lymph nodes were massed together and attached to the hilus. The tumor portion of the spleen was firm with a very irregular, nodular-like pattern, yellowish-white in color, and bordered by the more normal appearing purplish-red tissue. The capsule was thickened. On cut section the tumor involved nine-tenths of the entire specimen and was not encapsulated. It showed numerous irregular, firm, glistening, moderately smooth, pink to yellowish-white, small and large nodules. Areas of necrosis contained a thick yellowish-green material. The tumor appeared to involve a portion of the capsule. The attached lymph nodes were greatly enlarged by a growth similar to that shown in the spleen. Veins in the hilus, especially in the attached fat, were thickened and enlarged. One nodule appeared to be nonencapsulated.

Histologic examination revealed the architectural structure of the spleen preserved in part in some areas, with the usual malpighian corpuscles and richly cellular pulp. The capsule was thick and contained many erythrocytes, lymphocytes, and large mononuclear cells. In general the lymph follicles were of moderate size, and the central arterioles showed thickening and hyalinization. In other regions the normal structure of the spleen was destroyed, and the cells were distinctly atypical. In addition to very cellular areas there were areas of fibrosis, and scattered cells contained granular brown pigment. The atypical cells varied considerably in size; some were multinucleated with several large irregularly shaped,

deeply chromatic nuclei, while others were mononuclear in type and variable in appearance, most of them having abundant cytoplasm and large vesicular nuclei. Abnormal nuclei and mitoses were present in moderate numbers.

Sections of lymph nodes showed one small node to be relatively normal except for a few atypical cells in the central portion; the larger lymph nodes showed much destruction of the architecture with considerable fibrosis and atypical cells similar to those in the spleen. Some had acidophilic cytoplasm, and most had vesicular nuclei. Multinucleated cells were present but not abundant. Abnormal nuclei and mitoses were present in moderate numbers. Other sections of both the spleen and lymph nodes stained for reticulum showed numerous coarse reticulin fibers and connective tissue separating groups of the atypical cells. A few fine reticulin fibers were also present between some of the cells. Diagnosis was leukoblastosis of the spleen and lymph nodes, too undifferentiated to distinguish it as an anaplastic reticular cell sarcoma or a Hodgkin's sarcoma. The Sternberg-Reed giant cells (fig. 3) supported the latter diagnosis. Absence of involvement of any other lymph nodes than those of the splenic pedicle in conjunction with the histologic findings indicated that the tumor was a primary neoplasm of the spleen. This sarcoma appeared to be a mixed type, having features of both a reticular cell sarcoma and a Hodgkin's sarcoma.

The patient was last seen April 24, 1946. She was feeling well except for occasional spells of nausea and vomiting. The constipation, lower abdominal pain, and melena were

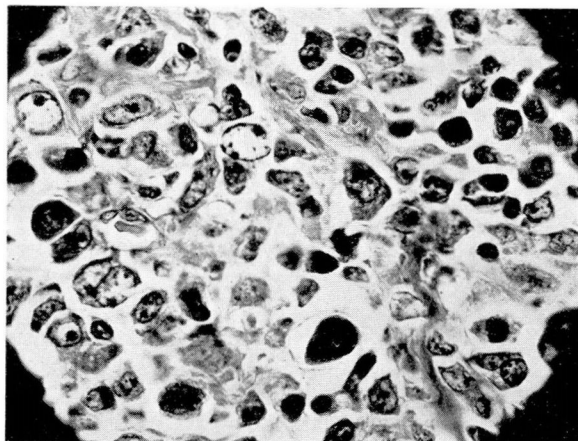


FIG. 3. Case 2. Microscopic section of spleen showing Sternberg-Reed giant cells (x850).

much improved. She may still suffer occasional nausea and vomiting because of the gall-bladder condition discovered at operation. No definite mass could be palpated in the abdomen. The esophagus, stomach, and duodenum were shown normal by x-ray examination. Routine kidney-ureter-bladder flat plate roentgenogram showed only moderate hypertrophic changes in the lumbar vertebrae. Red blood cell count was 4,690,000 with 11.5 Gm. of hemoglobin, and white blood cell count was 11,500. Differential count showed 78 per cent neutrophils and 22 per cent lymphocytes. X-ray therapy was advised because of the enlarged lymph nodes at the splenic pedicle, not all of which could be removed.

Discussion

The presence of Sternberg-Reed type giant cells in a primary splenic sarcoma is rare and appeared to us of even greater interest than the finding of the rare condition of primary malignant disease of the spleen. It was the presence of these cells without the presence of plasma cells and eosinophils that led to

the difficulty in classification of these tumors and made the various classifications suggested in the literature appear inadequate. In reviewing 131 cases described in the literature, we are able to find 15 primary splenic malignant tumors where multinucleated cells are mentioned without presence of typical Hodgkin's granuloma, and we cannot determine from the descriptions how many of these are the Sternberg-Reed type giant cells. Menétrier¹⁰ believed that the tumor which he named "splenoma" was derived from large mononuclear cells of the splenic cords. There were numerous giant cells containing inclusions of vacuoles. In areas not yet involved by the neoplasm an intense sclerosis, an endarteritis obliterans of the medium sized and smaller arteries, periarteritis, and disappearance or atrophy of the follicular elements were observed. A similar tumor was described by Foix and Roemmele,¹¹ who called it a nodular reticulo-splenoma and believed it to be derived from the reticular elements of the malpighian follicles. They believed a "round-cell sarcoma with giant cells" described by Simon (as cited by Smith and Rusk¹²) should also be classified splenoma. Duchemin¹³ described another such tumor as a primary sarcoma of the spleen, but Menétrier considered it in the splenoma group. Langenstrasse and Neumann¹⁴ described a primary endothelial sarcoma of the spleen, which classification Gerundo and Miller¹⁵ later challenged, since they considered that the tumor arose from the reticulum without any endothelial origin or nature, as the cells had no angioblastic activities. They believed that this tumor fitted into Menétrier's splenoma group. Grayzel¹⁶ described a reticular cell sarcoma of the spleen wherein an occasional tumor giant cell was seen. Smith and Rusk¹² described 9 endotheliomas with multinucleated giant cells. It is questionable whether these were of the Sternberg-Reed type.

The confusion of the various classifications as to the histologic diagnosis of primary malignancy in the spleen has been partially clarified by the adoption of the anatomic origin of the various neoplasms from splenic tissue. Bonney⁸ classifies five tissues of origin: "connective tissue in the splenic capsule; reticular stroma of the spleen; lymphoid tissue surrounding the arterial vessels as an interrupted sheath, known as the splenic nodule or malpighian corpuscles; endothelial cells in the walls of the blood vessels; and reticulo-endothelial cells lining the splenic sinuses."

Hausmann and Gaarde¹ classify the tissue of the reticular stroma and malpighian corpuscles both under "lymphoid elements which give rise to lymphoma and lymphoblastoma," and subclassify these as follows:

- A. Lymphosarcoma
 - 1. Large round cell (reticulum-cell type)
 - 2. Small round cell (lymphoblastic type)
 - 3. Giant lymph follicle hyperplastic
- B. Hodgkin's granuloma

Neither of these classifications allows for adequate nomenclature for tumors of a mixed type. It is with this fact in mind that the hypothesis recently advanced by Herbut, Miller, and Erf¹⁷ was noted with interest. They believe

that various combinations of Hodgkin's disease, lymphosarcoma, and reticulum cell sarcoma anywhere in the body can be explained only by considering the three diseases as arising from a common stem cell, the reticulum cell, and then differentiating in one direction or another according to the amount and type of stimulation. They present 6 cases which at one time were diagnosed as Hodgkin's disease and at another time as lymphosarcoma by biopsies and which at autopsy showed various combinations of Hodgkin's disease, lymphosarcoma, and reticulum cell sarcoma. They then describe the action of two substances, a myeloid stimulator (which can be separated into carbinols from the lipids of normal beef liver or the urine of patients with Hodgkin's disease or monocytic leukemia), and a lymphoid stimulator which can be separated into non-carbinols from the above materials. They further state that these substances appear to be mutually reciprocal when not in excess, "the myeloid stimulator causing the maturation of lymphoid cells, and the lymphoid stimulator causing the maturation of myeloid cells." Experiments on guinea pigs with these preparations are described. Herbut, Miller, and Erf suggest that lymphosarcoma might result from an excess locally of the lymphoid stimulator. They believe that reticulum cell sarcoma might result from an excess locally of both lymphoid and myeloid stimulators, each depressing the reciprocal maturing properties of the other so that stimulation of the common stem cell, the reticulum cell, might occur without maturation. Hodgkin's granuloma, according to these authors, might result from an excess of both stimulators but not in sufficient amount to preclude their reciprocal action and thus allow for a certain amount of maturation. The Sternberg-Reed tumor giant cell might then be derived from the common stem cell (reticulum cell), and the action of the stimulators on the blood-forming organs and connective tissue cells accounting for the proliferation, maturation, and destruction of many of the cellular elements of the blood and connective tissue that occur in Hodgkin's disease.

Final proof will probably depend on accomplishing the different procedure of tissue cell cultures and studying their response of the reticulum cell to these stimulator substances.

The derivation of these tumors from a common stem cell and their development by some variable combination of stimulators, together with the observation of a mixed cell type sarcoma and of varying cell types as different manifestations of apparently the same neoplastic disease, suggests to us the following modification of Class II of Hausmann and Gaarde's classification of primary neoplasms of the spleen, as a further clarification in classifying these tumors:

II. Lymphoblastomatous tumors arising from the common stem cell of the lymphoid and reticular elements, the reticulum cell.

A. Lymphosarcoma

1. Lymphoblastic (large round cell)
2. Lymphocytic (small round cell)
3. Giant follicular lymphoblastoma

B. Reticular cell sarcoma

- C. Hodgkin's granuloma and sarcoma
- D. Mixed type sarcoma
 - 1. Combinations of above cell types (mixed cell type)
 - 2. Manifestations of different cell types in different areas of growth.

In this modification the large round cell rather than the small round cell is considered as the lymphoblastic type of lymphosarcoma. Hodgkin's sarcoma is included, in addition to Hodgkin's granuloma, as a more cellular, wildly growing, invasive tumor (such as case 1 here presented) than the granuloma. The reticulum cell sarcoma is considered in a distinct class derived from the common stem cell, therefore not belonging to the lymphosarcoma class. Case 2 is best classified as a mixed cell type sarcoma, having manifestations in a single tumor of a reticular cell sarcoma and a Hodgkin's sarcoma.

Many authors have discussed the advisability of splenectomy and the prognosis of primary neoplasm following this procedure. Whenever the tumor is operable without evident metastases other than local glandular involvement, it is apparently the procedure of choice. Our one patient operated on has progressed well, but it is yet too early to venture a favorable lengthy prognosis.

Summary

1. A case of primary splenic sarcoma of Hodgkin's type and a case of mixed cell type sarcoma with some manifestations of Hodgkin's sarcoma, also primary in the spleen, are reported, bringing the total number of reported primary malignancies of the spleen to 190.

2. Modern classification of primary splenic malignant tumors is discussed as to the problem arising from the 2 cases presented. A possible modification of the classification presented by Hausmann and Gaarde of the Mayo Clinic¹ is suggested.

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