Extracutaneous Manifestations of Kaposi's Sarcoma

A Systemic Lymphoblastoma

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• **Kaposi's sarcoma may affect any system of the body. Serious difficulties occur only when the heart, lungs or gastrointestinal tract are affected. Usually, involvement in other viscera causes no clinical symptoms.**

This neoplasm is thought to be a low-grade lymphoblastoma. This idea of relationship is based on clinical and histologic association of Kaposi's sarcoma with the lymphoblastomas more commonly than would be anticipated from the rarity of the conditions under consideration. This concept is strengthened by the occasional seeming mutation of Kaposi's sarcoma into a lymphoblastoma. The associated reticuloendothelial hyperplasia in Kaposi's sarcoma is another link in the evidence of relationship.

ONE OF THE PLEASURES of dermatology is the occasional instance in which cutaneous manifestations are so accurately pathognomonic of obscure internal disease, that one is able to enlighten an internist or other overlapping specialist as to what ails a patient systemically. While most dermatologic patients have skin conditions only, there is the rare occasion when the dermatologist presents the key to unlock a visceral riddle. This has led to extensive study of such rare entities as necrobiosis lipoidica diabeticorum, acanthosis nigricans and a host of other cutaneous patterns in this category.

Kaposi's idiopathic multiple hemorrhage sarcoma is one of the more serious cutaneous entities. The possibility of visceral involvement has been recognized for many years by dermatologists but in a rather hazy fashion. Most skin specialists consider this condition to be comparatively benign, but it can be a threat to health and life.

The diagnosis of extracutaneous Kaposi's sarcoma must be made by x-ray examinations plus the observation of cutaneous lesions or by histopathologic study of surgical or postmortem specimens. Visceral involvement occurs in about 10 per cent of cases of Kaposi's sarcoma. According to Ellis,[9] 129,000 tumors were reported by 39 cooperating hospitals to the California Tumor Registry between 1942 and 1954. Only 21 cases of Kaposi's sarcoma were included, an incidence of 0.01 per cent. In only 14 of these cases had diagnosis been confirmed by histologic examination. In only one of these 14 was there visceral involvement. Undoubtedly visceral involvement would be noted in more cases if all patients with these tumors on the skin were followed to autopsy.

SITES OF INVOLVEMENT

Twenty-eight published reports of cases of systemic Kaposi's sarcoma were reviewed. The findings in those cases plus observations in seven cases reported for the first time in this communication constitute the material for this portion of the discussion.

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The gastrointestinal tract was involved the most frequently (23 cases or approximately 66 per cent). The lesions may occur in any portion from the lips to the rectum. Nodules within the easily visible oral cavity are not unusual. However, the stomach and intestines are the most common sites. Most subjects with Kaposi's sarcoma on the skin complain of intraabdominal pain even though roentgen ray examination may be negative. As a rule, the lesions are multiple. For instance, Dillard and Weidman[6] found more than a hundred blood-red tumors along the intestinal tract in a patient at autopsy. Seagrave[21] mentioned observing 44 nodules in 14 feet of small intestine. The lesions tend to be nodular and rounded or conical or mushroom-shaped. They involve the submucosa, seldom invading the musculature, so perforation is unexpected. On palpation the neoplasms are soft or semicystic. When seen through the epithelial covering or on cross-section, the tumors may be white or flesh colored or marbled with red and white or streaked or speckled by brown. They may be as much as 6.0 cm. in diameter. Symptoms are few. Hemorrhage is one of the more common. It is remarkable that this does not occur more frequently, for the neoplasm is vascular and is covered by only a thin layer of epithelium. Intestinal obstruction is less common and when it occurs it is likely to be partial. The tumors grow slowly, permitting adaptation by the adjacent normal tissues. Also, as they are soft and compressible, obstruction is uncommon. Loss of weight and vomiting seldom results from these growths. Lesions in the intestinal

tract seem to be more radiosensitive than those on the skin.

CASE 1. The patient was a 74-year-old man, born in Poland. About 20 years previously, Kaposi's sarcoma of the feet, legs, hands, wrists, ears, nose and tonsils had developed. After some five years, x-ray therapy had been given and the lesions were eradicated. There had been no cutaneous recurrence. The patient complained of "stomach" pains for at least 25 years. Gastrointestinal roentgen studies were consistently negative for abnormalities. The intraabdominal condition had been classified by various internists by a host of appellations ranging from "ulcer" to "amebiasis." The symptoms had not been disabling to the patient.

In June 1956, severe gastrointestinal hemorrhage from the rectum occurred. Tarry stools and bright red blood were passed. The patient was hospitalized immediately but despite conservative measures the bleeding continued. From 1,000 to 1,500 cc. of whole blood was required daily to maintain the blood volume and cellular constituents. The patient vomited once but there was no blood in the vomitus. X-ray studies showed a lesion in the second part of the duodenum. X-ray therapy to the abdomen was carried out and within 24 hours the bleeding stopped. There has been no recurrence to date.

Visceral lesions may be present without cutaneous tumors, as in the following case.

CASE 2. An 80-year-old man had had epigastric pain intermittently for ten years. A preoperative diagnosis of duodenal ulcer had been made. On surgical exploration, an area of thickening and scarring was found in the prepyloric area. Subtotal gastric resection and gastrojejunostomy were done. Upon microscopic examination of the removed specimen, a healed prepyloric ulcer and diffuse involvement of the stomach by Kaposi's sarcoma were observed. Acute hemorrhage developed on the sixth postoperative day. The possibility that the bleeding might be due to duodenal involvement with this tumor was considered. Roentgen irradiation, 1,000 r in divided doses was given to the area and the bleeding promptly stopped. Recovery was uneventful.

Next in frequency of involvement is the reticuloendothelial system. The liver was affected in 11 of the 35 cases reviewed, and the spleen in four instances. These structures are considered together since the changes are similar. Usually the involved organ is enlarged. Commonly, both viscera are affected in the same patient. There may be evidence of cirrhosis or even Banti's syndrome (see Case 4). Nodules of Kaposi's sarcoma may be noted in both organs. However, reticuloendothelial hyperplasia is not uncommon. The same changes may be found in the lymph nodes. These structures (superficial or deep) were observed to be enlarged in eight patients. Probably such enlargement is more frequent than is indicated by these figures. It occurs with or without ulceration of the cutaneous lesions. The changes found at operation or autopsy were identical with those seen in other organs of the reticuloendothelial system—that is, tumor or reticuloendothelial hyperplasia or both. It must be emphasized that hyperplasia of the reticuloendothelial system may occur in this condition in the absence of tumor nodules. The mediastinal or intraabdominal nodes were affected in most instances of visceral Kaposi's sarcoma in which surgical operation or autopsy was done.

CASE 3. A 53-year-old man, who had had extensive Kaposi's sarcoma of the arms and legs for 25 years was admitted to hospital two weeks after fever and coughing developed. On examination moist rales throughout his lung fields were noted. There was generalized superficial lymphadenopathy. The liver and spleen were enlarged. Moderate jaundice was present. Erythrocytes numbered 1,500,000 per cu. mm. of blood. At postmortem examination Kaposi's sarcoma of the skin, thyroid, ilium and lungs and of the hilar, retroperitoneal and iliac lymph nodes was observed.

Surprisingly, the genitourinary system was involved in seven instances—the kidneys in three cases, the testes in two and the urethra and bladder in one each. There were few signs or symptoms during life to suggest invasion of this tract. In the patient with the urethral lesion, stricture developed. In all instances, the involvement was manifested by tumors in the organs in question.

Bones were involved in six of the 35 cases here reviewed. This included the vertebrae, hands, legs and feet. These lesions were tumors arising from extension of the cutaneous masses or neoplasms developing independently within the osseous structure. According to Cajaffa,[3] bone involvement is frequent in Kaposi's sarcoma. He found it in all three cases he studied and expressed the belief it was due to increased circulation through the skeletal system resulting from overlying cutaneous tumors. However, he was concerned with osteoporosis which could have resulted from the age and general condition of the patients he studied. In the case reported by Ronchese and Kern,[17] cystic areas of rarefaction were found in the medulla of the fingers and toes. The investigators believed that such lesions were not due to increased circulation, since there was no rarefaction under large tumor masses, or to extension from overlying neoplastic growths since there were no such lesions over the rarefied areas. Most of the lesions of the bone were proved to be neoplastic by autopsy examination.

The respiratory system including the trachea, bronchi, pleura and parenchyma of the lungs was affected in eight instances. Commonly the lesions were multiple. The symptomatology was that of an intrathoracic tumor and depended on the exact loca-

tion and size of the new growth. Cough, hemoptysis, pleurisy and loss of weight were common, but in some reported instances there were no such symptoms. Roentgen examination showed multiple lesions in those instances in which such investigations were performed. The conditions observed roentgenographically may simulate those of pneumonia, tuberculosis or tumor. Results of bronchoscopic examination, carried out in two cases, were negative, as were examination of pulmonary secretions by the Papanicolaou method.

CASE 4. The patient, a 67-year-old man, had noticed weakness in 1947 and upon examination at that time enlargement of the spleen and anemia were noted. In 1949, Kaposi's sarcoma developed on the feet, legs and penis. The diagnosis was made clinically and confirmed by histologic examination. On examination in August 1951, in addition to the already noted conditions, enlargement of the liver was observed. About a month later, a splenic infarct developed, possibly secondary to cortisone therapy. At about that time a cough was noted, accompanied by mucopurulent sputum. The lung fields, which had been clear, now showed inspiratory rales and decreased breath sounds and fremitus over the right lower lung fields. Thoracentesis was carried out and 150 cc. of sterile straw-colored fluid was withdrawn. Roentgen examination showed a mottled process scattered throughout the right lung fields, suggestive of sarcomatosis. This condition improved with x-ray therapy. The patient also had a leukopenia (as few as 950 leukocytes per cu. mm.). About a year later, the patient killed himself by jumping out of a window. At the coroner's autopsy involvement of the right lung and peritoneum by nodules of Kaposi's sarcoma was noted and there was reticuloendothelial hyperplasia of the liver and spleen.

Cavities may be noted in the lung, as in the following case.

CASE 5. A 76-year-old man, first noted multiple nodules on the left foot in 1950. In March 1954 a severe cough and hemoptysis developed. Roentgen ray examination revealed a diffuse infiltrating process throughout the right lung. Cavitation was a prominent feature. There was little or no response to x-ray therapy.

In April 1954, the patient was admitted to the hospital with left pneumothorax and incomplete aeration of the right lung due to partial occlusion of the main stem bronchus. This was followed by pronounced subcutaneous emphysema. The condition of the patient continued to deteriorate and he died in June 1954. At autopsy nodules and cystic cavities in the lungs, an ulcerated nodule in the stomach, 21 nodular, ulcerated or polypoid lesions in the jejunum and ileum, a nodule in the perirenal sac of the left kidney, a tumorous nodule in the pancreas and tumor involvement throughout the parietal region of the brain plus involvement of the cerebellum on the right side in the region of the dentate nucleus were observed. The lesions were histologically identified as Kaposi's sarcoma. In addition there was medullary hyperplasia of the adrenals, and reactive hyperplasia and tumor formation in the lymph nodes.

The endocrine system was affected in six cases—the pancreas in two, the thyroid in two and the adrenal glands in two.

CASE 6. The patient, a 54-year-old man, had a lesion on the leg of three years duration which had been diagnosed by study of a biopsy specimen as an epidermoid carcinoma. The lesion responded poorly to irradiation. The condition of the patient deteriorated and he had lost 35 pounds in the two months before the present examination. Hemoptysis and cough had developed two weeks previously. On physical examination, rales and dullness at the base of both lungs were noted. The heart sounds were faint. Subcutaneous masses were noted on the abdomen and chest. There was pronounced enlargement of inguinal lymph nodes. The hemoglobin value was 35 per cent and erythrocytes numbered 1,900,000 per cu. mm. There were 18,350 leukocytes per cu. mm. At autopsy, tumors of Kaposi's sarcoma were observed involving the skin, lungs, small intestines (multiple nodules), omentum and both adrenal glands.

An interesting observation in this respect was the report by Hurlburt and Lincoln[10] pointing out that Kaposi's sarcoma may coexist with diabetes mellitus. The obvious inference is that the latter is secondary to the neoplasm. However, it seems unlikely that the tumor would destroy the entire gland or would selectively invade the islets of Langerhans. In the only one of the cases studied by Hurlburt and Lincoln in which autopsy was done, the changes in the pancreas were considered to be on a vascular basis. As Ronchese and Kern[18] pointed out, probably the relationship is more coincidental than real. None of the patients in the present study had diabetes. Involvement of the thyroid and adrenal glands was "silent" clinically also.

The heart was the site of tumors in five instances. Weller[23] expressed belief that cardiac involvement could be diagnosed clinically by a definite chain of symptoms and signs. He described this as an acute upper respiratory infection which became subacute and was manifested by cough, malaise, night sweats, sputum and hemoptysis. He mentioned edema of the face and cyanosis as other characteristics. Fever also was common—as high as 101°F. in some cases. In all cases in which x-ray examination was done, a tumor in the right auricle with pericardial effusion was observed. Choisser and Ramsey[5] reported two instances of tumor occurring in the right auricle, causing a ball-valve type of obstruction at the tricuspid orifice and bringing about rapid death. However, cutaneous lesions were

not present in the cases reported by Weller and by Choisser and Ramsey, and it is possible the tumors were of another type, although histologically resembling Kaposi's sarcoma. In fact, the tumors in those instances might be better classified as angioreticuloendotheliomas rather than as Kaposi's sarcoma. Tumors may occur in any part of the heart in association with cutaneous manifestations and may cause pericarditis, effusion, heart block, arrhythmia or cardiac failure.

CASE 7. The patient, a 77-year-old man, had a long medical history of serious conditions requiring operation, and of refusal to submit to operation. Included were ulcerative colitis, acute cholelithiasis, adenocarcinoma of the rectum and prostatic hypertrophy. He also had complete heart block. Cutaneous nodules developed in 1948. The patient was admitted to hospital in February 1952 because of bloody vomitus of 24 hours' duration. On examination, it was believed he was uremic with hemorrhagic diathesis. Suprapubic prostatectomy was attempted but the patient died on the operating table. At autopsy involvement of the heart was noted (nodules in the fatty portion, in the left ventricle, and in the tricuspid valve), also nodules in the small intestines (especially in the duodenum) and tumor masses in the adrenals and in the lymph nodes. Microscopic examination showed all these lesions to be Kaposi's sarcoma.

The brain was invaded in one instance and the spinal column in one.

The conjunctiva was a site of involvement in one case.

Muscles are affected occasionally by extension from the skin or by independent tumors.

LABORATORY FINDINGS

Other than histopathologic and roentgen-ray examination, laboratory studies have not been productive of diagnostic tests. Mild to severe anemia is common. This may be the presenting symptom, as in Case 4. In the presence of pulmonary or, more commonly, gastrointestinal hemorrhage, hemoglobin and erythrocyte values may fall to extreme lows. In such instances, transfusions may be imperative. Mild eosinophilia is common. Leukocytosis—15,000 to 20,000 cells per cu. mm.—may be present, or there may be leukopenia, as in Case 4. Frequently there is an increase in monocytes and transitional cells. The differential count may show as many as 60 per cent Flarer cells (abnormal monocytic cells shifting toward the lymphoid series). However, this phenomenon is not found in all cases nor is the presence of this cell pathognomonic of Kaposi's sarcoma. The bone marrow may be hyperplastic, with an increase in mononuclear or reticuloendothelial cells.

Abnormalities in the urine, stool, vomitus and effusions are those associated with a tumor in the involved organ. Usually no abnormal cells are demonstrable by the Papanicolaou method. Results of liver function tests vary, but if there is severe hepatic involvement, damage may be indicated by such tests.

RELATIONSHIP TO LYMPHOBLASTOMAS

Since Kaposi's sarcoma, lymphoblastomas and leukemias are all unusual conditions, the frequent coexistence of these entities must be given consideration beyond that ordinarily paid to the presence of two or more of the commoner diseases in the same host.

CASE 8. A 73-year-old man, had respiratory tract disease diagnosed as bronchopneumonia in November 16, 1952. The temperature was 102°F. and coarse rales were heard in the right lung fields. These symptoms abated when penicillin was given parenterally. However, three or four days later there was a recurrence of fever and an area of consolidation was noted at the base of the lung on the right side. The conditions improved when aureomycin was administered by mouth, but the patient coughed constantly and commenced to expectorate large amounts of mucoid sputum tinged with blood. Upon roentgen examination, partial consolidation of the right lung and pleural effusion were noted. At about this time cutaneous lesions diagnosed clinically and by biopsy as Kaposi's sarcoma developed on the lower limbs and on the left lower eyelid. The lesion on the eyelid responded temporarily to x-ray therapy. The pulmonary condition persisted and the cutaneous lesions became more pronounced. The patient died September 9, 1953. At postmortem examination, Hodgkin's disease confined to the right lung and pleura was observed, in addition to the cutaneous lesions of Kaposi's sarcoma.

In a review of the literature in 1954, Pack and Davis[14] found reports of seven cases of Kaposi's sarcoma associated with Hodgkin's disease or leukemia or mycosis fungoides. They added reports of two additional cases in which giant follicular lymphoma (Brill-Symmers disease) was associated with Kaposi's sarcoma. Allen[1] stated that in a review of the literature he had found reports of 15 cases in which Kaposi's sarcoma and a lymphoma were present in the same patient. In five of those cases the lymphoma was Hodgkin's disease, in four lymphatic leukemia, in three lymphosarcoma, in two mycosis fungoides and in one myelogenous leukemia. Allen also noted that in seven of 41 cases of Kaposi's sarcoma studied at the Memorial Cancer Center, the patient had lymphoblastoma also. This is an association of about 17 per cent, a very high figure indeed. He reported on eight cases in which lympho-

blastoma was present (the seven cases already mentioned and one other that he studied elsewhere). In four of the eight it was Hodgkin's disease, in two mycosis fungoides, in one lymphosarcoma and in one reticulum-cell sarcoma. Independent lesions of both diseases were found in some patients, while in others histologic study revealed changes of both conditions within the same cutaneous or lymph node tumor. The association of these two pathologic conditions in the same lesion was reported by Rosen[19] in 1943 and later (in the same patient) by Sachs and Gray.[20] Lane and Greenwood[11] reported on a patient with Kaposi's sarcoma, mycosis fungoides and lymphatic leukemia. Therefore, it seems possible that Kaposi's sarcoma may be a low-grade lymphoblastoma that may undergo mutation to resemble one of the other members of the group. It is well known that mycosis fungoides, Hodgkin's disease, lymphosarcoma and other more malignant forms of this group may do this. The frequency of hyperplasia of the reticuloendothelial system with lymphadenopathy, hepatomegaly and splenomegaly in Kaposi's sarcoma adds weight to this concept.

Histopathologists recognize four stages of Kaposi's sarcoma—inflammatory, angiomatous, granulomatous and sarcomatous. It is possible that a fifth stage, lymphoblastomatous, may occur in this condition.

To get the opinion of others, seven of the leading dermatopathologists were asked two questions: Is the histopathology of Kaposi's sarcoma and the lymphoblastomas so distinct that it would be impossible to confuse the two? Could it be that there is a fifth, a lymphoblastomatous, histologic stage in Kaposi's sarcoma?

On the whole, all seven preferred to believe that the conditions under consideration should be considered as distinct. Yet, selected sentences lifted out of the context of their replies might give a different interpretation. As examples:

Beerman[2] said, "You may be right that there is a fifth phase of Kaposi's sarcoma, but I have never seen it." To quote Winer,[24] "Now then, being all of reticuloendothelial origin [he was speaking of the lymphoblastomas and Kaposi's sarcoma], there are stages in these conditions which may be mistaken for each other." And again, "I have never seen a Kaposi's sarcoma go into a lymphoblastomatous phase, and I doubt that it could . . . yet, it is an interesting thought." Montgomery[13] observed, "Kaposi's sarcoma can terminate as a reticulum cell sarcoma or possibly even as a hemangio-endothelioma." And, "It is foolish to try to draw too sharp lines of distinction, as there are so many variants." Pinkus[16] contributed, "I would favorably consider the hypothesis that lymphoblastoma might develop in Kaposi's, possibly not as a fifth stage beyond the sarcomatous one, but rather as a side branch." Caro[4] said, "All aspects and interrelationships of the lymphoma group are still very confused." Only Lever[12] and Weidman[22] refused to consider this possibility. Weidman pointed out, "Once again, Kaposi's sarcoma being so essentially vascular, I think that one is stretching things too much to contend for a lymphoblastomatous stage on the basis of histologic changes." To summarize then, it is no more possible to relate the true lymphomas and Kaposi's sarcoma on purely histologic grounds than it is on the basis of strictly clinical changes. However, putting all the evidence together, there is a strong suggestion that this sarcoma should be included in the lymphoma group.

In separate correspondence regarding Case 1, Pack[15] stated, "I believe the two diseases (lymphoma and Kaposi's sarcoma) are related, that is to say, that they are both manifestations of a disorder of the reticuloendothelial system." Dorffel[7] felt that Kaposi's sarcoma was a reticuloendotheliosis on histologic evidence.

In order to establish whether Kaposi's sarcoma should be considered as a lymphoblastoma, one must define this group of diseases. Perhaps Eller's[8] concept is as good as any. He stated: "The term *lymphoma* has been applied to a group of diseases, the etiology of which is unknown. They are characterized by proliferation of lymphatic or reticuloendothelial tissue which may occur in the skin as well as in any other organ of the body." Acceptance of this definition would suggest that Kaposi's sarcoma should be included in this group after consideration of the previously offered facts.

All in all, there is too much evidence to ignore the possible relationship between the lymphoblastomas and Kaposi's sarcoma. If Kaposi's sarcoma cannot undergo mutation into a fifth or side stage that histologically resembles a lymphoblastoma—and it has not been established that this is impossible—then it might have common etiologic factors with these other poorly understood neoplasms. Certainly, all these conditions can be grouped under the heading of reticuloendotheliosis. Every factor that has been considered would lead to this conclusion.

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