Clinical Experience

Aggressive Behavior of Classical Kaposi’s Sarcoma and Coexistence With Angiosarcoma

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An 82-year-old Caucasian man presented with initially asymptomatic livid red plaques on the plantar surface of the feet that become confluent and evolved into invasively growing nodules accompanied by massive edema. Histology allowed a diagnosis of the classical form of Kaposi’s sarcoma: the serology test result for HIV was negative, whereas the associated human herpes virus type 8 was detected by polymerase chain reaction on the skin sample. Over the subsequent 6 months, skin lesions become vegetative and partially necrotic, and extended to the hands and eyelids. Chemotherapy with vinblastine appeared to stabilize the cutaneous disease, but the patient developed a massive gastrointestinal hemorrhage secondary to dissemination to the stomach. Twelve months after the onset of the disease, vegetative and easily bleeding lesions progressively occluded the mouth of the patient: histological features were consistent with a low-grade angiosarcoma distinct from that of Kaposi’s sarcoma. The patient could not chew and swallow anymore; he was put on an artificial nutrition but died shortly thereafter. This case illustrates that, even in its classical form, Kaposi’s sarcoma may be a malignant, rapidly progressing tumor.

Learning Points. a) The extent and rate of spread of initial skin lesions should be considered to be early signs of aggressive dissemination, even in the absence of other variables (i.e., histological pattern, human herpes virus type 8 positive mononuclear cells) associated with progression of the disease. b) An endoscopy may be useful given the high prevalence of gastrointestinal involvement. c) When classical Kaposi’s sarcoma displays aggressive behavior a second, primary malignant tumor arising from the vascular tissue should be investigated.

Take-Home Message. Even in its classical form, Kaposi’s sarcoma may be a malignant, rapidly progressing tumor with visceral involvement; also, a second malignancy may occur in nearly one patient of four. Because localized skin lesions can regress completely with radiotherapy, watchful waiting is probably inappropriate in most cases.

Classical Kaposi’s sarcoma is a rather sporadic angioproliferative disease, particularly prevalent among people of Mediterranean, Eastern-European, and Jewish ancestry, that generally affects older persons, predominantly males (1–3). It begins with skin lesions usually confined to the lower extremities, but with possible centripetal progression. These lesions are characterized initially by livid red, plain maculas or patches. In the course of the disease, elevated plaques and solid nodules (millimeters to centimeters) can develop and, when confluent or invasively growing, they are usually accompanied by edema. Spontaneous bleedings in the environment of the tumors are typical. As for all the forms of Kaposi’s sarcoma, human herpes virus type 8 (HHV-8) is believed to be the primary cause (6,7). However, classical Kaposi’s sarcoma is considered a less malignant, slowly progressing tumor (8,9). Because of the advanced age at onset of the disease, it has been documented that patients usually die of other illnesses. Evidence of aggressive behavior of classical Kaposi’s sarcoma has been occasional, and the association with another malignant tumor linked to HHV-8 infection has only been suspected.

Case Report

The patient was an 82-year-old man from Puglia, a southern region of Italy along the Mediterranean Sea. He had been a construction worker for over 50 years, and he had never married. A previous smoker, he was well, active, and completely independent without active medical problems except for stage 1 hypertension.

The patient came to our attention because of painful skin lesions which appeared 2 months earlier as asymptomatic livid red plaques on the plantar surface of the left foot. On examination, the surface was occupied by confluent purple-red plaques and invasively growing nodules with areas of yellow-greenish discoloration alternating with hyperkeratotic forms. Body temperature was normal, and blood pressure was 130/70 mmHg. Complete blood cell count revealed only a minor reduction of hemoglobin level (Hb 10.8 g/dl). Renal function, hepatic function, electrolytes, chest X-ray, electrocardiogram, and urinalysis were all normal. A skin biopsy showed a tumor developing in the middle and upper
dermis with spared epidermis. Around physiological dermal vessels and appendages, there were new thin-walled, slit-like vessels with localized extravasated erythrocytes, hemosiderin deposits, and an inflammatory infiltrate of macrophages. A mixed pattern of angiomatous and spindle cells was evident on stain with hematoxylin and eosin. The serology test result for HIV was negative, whereas HHV-8 was detected by polymerase chain reaction on the skin sample. A diagnosis of classical Kaposi’s sarcoma was made (Figure 1C). No specific treatment was deemed necessary other than accurate cleaning of the lesions.

One month later, lesions had disseminated to cover almost entirely the plantar surface of the feet (Figure 1A), and extended to the left eyelid and to the left hand (Figure 1B). The patient was reporting a persistent painful, burning sensation at the lower extremities; bilateral, tender peripheral edema was present in conjunction with inguinal lymphatic node enlargement. Because ultrasonographic features appeared consistent with the localization of Kaposi’s sarcoma, no biopsy was performed. Instead, the lesions on the eyelid were removed, and systemic, single-agent chemotherapy with vinblastine (6 mg/m²) every 4 weeks was initiated. Chemotherapy was well tolerated for eight consecutive cycles, and appeared to stabilize the cutaneous dissemination. Renal function had deteriorated slightly (blood urea nitrogen [BUN] = 65 mg/dl, creatinine = 1.3 mg/dl); hemoglobin level was 12.0 g/dl.

Eleven months after the onset of the disease, a massive gastrointestinal hemorrhage was diagnosed. Hemoglobin level fell to 4 g/dl and platelet count was 213,000/mm³, so multiple blood units were transfused. At gastroscopy, the gastric fundus was occupied by several nodular lesions with angiomatous features that were bleeding spontaneously. Multiple biopsies confirmed the visceral involvement by Kaposi’s sarcoma. Hemoglobin level rose to 7.9 g/dl, but general conditions had deteriorated to such an extent that the patient had to be admitted to a nursing home. Chemotherapy was not resumed because of the continuous blood loss and need of transfusions.
Meanwhile, skin lesions were rapidly increasing in number and size, especially in the hands (Figure 1B). Some of them had become necrotic, or ulcerated with bleeding; purulent secretion was also present, predominantly in the feet.

Shortly thereafter, approximately 12 months after the onset of the disease, the mouth of the patient was progressively occluded by vegetative lesions (originating from the hard palate) that were easily bleeding. Examination of one lesion (4.7 × 2.2 cm) expelled spontaneously with cough documented histological features consistent with a low-grade angiosarcoma distinct from that of Kaposi’s sarcoma (Figure 1D). Immunohistochemical stain showed cells positive for CD31, CD34, and Factor VIII-related antigen. The patient could not chew and swallow anymore; he was put on an artificial nutrition but died within few days. Autopsy was not performed.

**DISCUSSION**

In classical Kaposi’s sarcoma, skin lesions can remain unchanged for years; the disease usually has a chronic, indolent clinical course over many years, and is not life-threatening. However, lesions can increase in number and size and spread out, although metastases, in a strict sense, do not occur. In some instances, classical Kaposi’s sarcoma can show a slow centripetal progression with possible dissemination to other organs. On the basis of a retrospective analysis of 248 cases, Brenner and colleagues (10) have found that in 18% of cases there is a centripetal progression from a local to a diffuse skin involvement with a median time of 22.4 months (range 2–156 months). In less than 4% of patients, classical Kaposi’s sarcoma has visceral spread with a median time of 33 months (range 2–192 months) (10). Of many variables (sex, ethnicity, number of lesions, anatomical distribution, immunosuppression, initial management) tested as possible indicators of progression, none has proved discriminating except older age (>50 years). In addition, the finding that observation alone does not seem to be a negative prognostic factor is usually taken to indicate that the approach of “watchful waiting” can be the primary management for selected older patients with classical Kaposi’s sarcoma. Indeed, patients diagnosed in their 7th–8th decade of life die typically of other causes. Death from Kaposi’s sarcoma has been reported to occur in 1.6%–9% of cases, from 2 to 5.7 years after the onset of the disease (10,11).

In our case, the patient was diagnosed at the age of 82 when he was otherwise well, active, and completely independent. None of the presenting characteristics was considered alarming, and the patient was reassured about the long-term prognosis. Indeed, there are not definitely identified prognostic factors for progression of the disease (see Table 1). Lospalluti and colleagues (11) have shown that there appear to be three subsets of classical Kaposi’s sarcoma based on the extent and rate of spread at initial diagnosis, and characterized by substantially different survival times. However, their study was retrospective, and the criteria applied were inferential. Also, there is circumstantial evidence that involvement of sites other than extremities, especially viscera, is associated with a more aggressive entity (10). Bisciglia and colleagues (8), instead, in a large clinicopathological overview describing the progression of the disease, have distinguished six major histological patterns: inflammatory, granulomatous, predominantly angiomatous, predominantly spindle cell, mixed, and anaplastic. These different patterns as well as the presence of variant forms may have prognostic value (8,12). Finally, although DNA sequences of HHV-8 can be detected in both skin lesions and peripheral blood cells, detection in the mononuclear blood cells appears to predict more aggressive clinical behavior. Boneschi and colleagues (13), studying 40 patients with classical Kaposi’s sarcoma, have documented that HHV-8 DNA sequences were found in 41% of patients with slowly evolving disease as opposed to 74% of those with rapidly evolving disease. Certainly, our case illustrates a tumultuous dissemination of the disease despite: a) the absence of obvious visceral involvement at the onset, b) the more favorable mixed pattern of angiomatous and spindle cells, and c) no evidence of HHV-8 DNA sequences in peripheral mononuclear blood cells.

In our patient, there was histological confirmation of gastric involvement by classical Kaposi’s sarcoma. Although gastrointestinal involvement is believed to be very common, there are only few data available. With the exclusion of sporadic case reports (14,15), there is only one study using endoscopy. In a series of 87 patients with classical Kaposi’s sarcoma, Lospalluti had found signs in the stomach (16). Additional lesions were detected in the esophagus and in the proximal duodenum. Yet, gastrointestinal involvement is usually asymptomatic and only rarely a cause of hemorrhage. A single case of massive bleeding has been reported; that case occurred in a patient with stable cutaneous lesions (14). Later in the course of the disease (a few weeks prior to death), the patient was diagnosed with a low-grade angiosarcoma of the mouth.

Classical Kaposi’s sarcoma seems to be associated with a higher incidence of second malignancies (17). Lospalluti and colleagues (11) have reported two cases of lung carcinoma, one case of prostate carcinoma, and one case of Hodgkin’s lymphoma in 163 cases of classical Kaposi’s sarcoma. Bisciglia and colleagues (8) described three cases of Hodgkin’s lymphoma, one case of monocytic leukemia, and one case of peripheral T-cell lymphoma. In a recent retrospective analysis of 248 patients (10), 19% had second malignancies, most frequently adenocarcinomas and lymphoreticular disorders. However, the simultaneous occurrence of classical Kaposi’s sarcoma and angiosarcoma has been reported in only one case (18). Like Kaposi’s sarcoma, a significant percentage of angiosarcoma has been associated with HHV-8 infection (19) but, although apparently similar in some aspects, the two conditions have distinct histological features. In our case, the histological distinction was based on the International Classification of Diseases for Oncology (20) and on the immunohistochemical characterization (21).

Classical Kaposi’s sarcoma is strikingly radiation sensitive. Radiotherapy is the treatment of choice for localized lesions, with a rate of regression between 80% and 90% (22). The intralesional treatment with vinca alkaloids or interferon allows high antiproliferative concentrations directly into the tumor and is regarded to be a feasible alternative (23). In our case, neither radiation nor intralesional chemotherapy could be considered because of the dissemination of lesions. Instead, we treated our patient with systemic chemotherapy as is usually recommended.
for patients with disseminated disease. Excellent results and tolerable side effects have been reported with single-agent and combination chemotherapy regimens. Vinblastine, in particular, has been associated with response rates of 73%–90% (24,25). Time to response is 4–10 months, and the duration of response for all patients was 27 months (41 months for complete responders and 15 months for partial responders). Treatment results are unaffected by the patients’ age, sex, ethnicity, previous treatment, and the extent of the disease. In our case, vinblastine was initiated as a single agent 3 months after the onset of the disease, and was continued every 4 weeks for eight cycles, with an apparent stabilization of the cutaneous disease. More recently, paclitaxel—a microtubule-stabilizing agent highly effective against several tumors, including ovarian, breast, and lung carcinomas—has been shown to be active in Kaposi’s sarcoma (26). Other treatment modalities including pegylated liposomal doxorubicin and human choric gonadotropin are also highly effective in the treatment of disseminated diseases (27,28). In our case, we could not start a second-line treatment because the conditions of the patient deteriorated rapidly owing to persistent bleeding requiring subsequent blood transfusions. Different class I interferons (alpha 2a, 2b, beta) have been used in varying doses and intervals in the treatment of classical Kaposi’s sarcoma (29). However, despite reported remission rates of 60%–70%, a standardized treatment scheme does not exist at present. Finally, results from preclinical studies indicate that highly active antiretroviral therapy including protease inhibitors has potent and direct antiangiogenic and anti-Kaposi’s sarcoma activities in both HIV-positive or HIV-seronegative individuals (29).

Summary

There are cases of classical Kaposi’s sarcoma that defy the definition of tumor with slow progression, hardly interfering with the quality and life expectancy of the patient. Unfortunately, there are only weak prognostic factors for aggressive behavior. Patients with classical Kaposi’s sarcoma displaying aggressive behavior should be examined for a second, primary malignant tumor arising from the vascular tissue.

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