

## Widespread purple-brown cutaneous plaques and nodules

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### SELF-ASSESSMENT QUIZ

A 50 year old man with end stage renal failure was started on hemodialysis in 1995. In January 1997, he underwent renal transplantation. He started an immunosuppressive regimen which included cyclosporine A and prednisone after the transplantation.

He had two rejection episodes which were treated with a 3-day course of intravenous methylprednisolone. One and half years post-transplantation, in late July 1998, while the patient's renal function remained stable, he noted the onset of indolent smooth-surfaced red-purple nodular lesions on the dorsum of his right foot (Fig. 1). After one month, sev-



Figure 1. Indolent smooth-surfaced red-purple nodular lesions on the dorsum of the right foot

eral new purple-brown skin plaques and nodules appeared on his face, neck, trunk and hands (Fig. 2). An excision biopsy was performed. Microscopically, the section of skin demonstrated aggregates of newly formed blood vessels, with large protruding endothelial cells. There were narrow vascular slits and proliferation of spindle shaped cells. There was an extravasation of red cells, with

hemosiderin deposition. Also there was mixed inflammatory cell infiltrate of lymphocytes and histiocytes. Serology for HIV, Hepatitis B virus, Hepatitis C virus, and Epstein-Barr virus were negative.



Figure 2. Purple-brown skin plaques and nodules on the left upper eye lid, cheek and the neck

### Questions

1. What is your diagnosis?
2. Is this condition common in renal transplant recipients?
3. What is the cause of this condition in post-transplant patients?
4. What is the classification of this condition?
5. What is the differential diagnosis of this condition?
6. How should this condition be treated?

(Please turn to next page for answers.)

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## Answers

### 1. What is your diagnosis?

The diagnosis is iatrogenic cutaneous disseminated Kaposi's sarcoma (KS).

### 2. Is this condition common in renal transplant recipients?

Yes. Warts and skin tumors are common in renal transplant recipients. An epidemiological study showed a 400 to 500-fold increase in the incidence of Kaposi's sarcoma in these patients compared with control subjects of the same ethnic origin. 60% of transplant patients with KS show involvement of the skin or oropharyngolaryngeal mucosa, or both.<sup>1</sup>

### 3. What is the cause of this condition in post-transplant patients?

The cause of post-transplant KS remains unknown. Besides immunosuppression, other factors such as genetic predisposition and oncogenic viruses, particularly HHV-8, seem to be involved.<sup>2</sup> Since approximately 75% of patients with non-visceral lesions have complete or partial remission of their cancers after stopping or reducing cyclosporin-A therapy, KS may be the consequence of increased skin susceptibility to immunosuppressive treatments.<sup>1</sup> Different alterations of Langerhans cells have been reported in renal transplant patients treated with cyclosporin-A compared to those treated with azathioprine. Therefore, the specific action mechanism of cyclosporin-A may be an essential condition for promoting KS.<sup>3</sup> Recent data demonstrate a risk of transmission of HHV 8 through kidney transplantation.<sup>2</sup>

### 4. What is the classification of this condition?

Kaposi's sarcoma is classified into four groups: endemic, epidemic (or AIDS-related), classic, and iatrogenic.

The endemic type has been described in certain areas of Africa, while the epidemic type is common in homosexual men or drug abusers who are infected with HIV.<sup>4</sup> Endemic KS exhibited four clinically distinct forms: benign nodular, aggressive, florid, and lymphadenopathic. The male to female ratio of the benign nodular, aggressive, and florid forms was approximately 17:1, whereas that of lymphadenopathic KS was 3:1. The lym-

phadenopathic KS, a unique pediatric variant of KS occurring exclusively in black African children between the ages of 1 and 15, is generally fatal within 1 to 3 years of onset.<sup>5</sup>

The classic type is seen more often in people of Jewish or Mediterranean descent, and shows a predilection for males (male-female ratio, 2:1 to 3:1).<sup>4</sup> The lesions generally occur on the legs, and rarely involve the viscera.<sup>5</sup>

Iatrogenic disease is associated with immunosuppressive therapy, especially in cases of patients receiving immunosuppressive medications for autoimmune disease, cytotoxic chemotherapy for cancer, or cyclosporin A (Neoral, SangCya, Sandimmune) after organ transplantation.<sup>5</sup> These lesions are most often localized to the skin, appearing as early as 2 months and as late as 8 years after initiation of immunosuppressive therapy. In some patients, the KS lesions regress after termination of immunosuppressive drugs. The male to female ratio of this type of KS is approximately 2.3:1.<sup>5</sup>

The AIDS-associated form of KS (AIDS-KS) can be aggressive, and often results in dissemination and invasion of lymph nodes and viscera (gastrointestinal tract, lungs, liver, kidneys, or spleen). The widespread cutaneous and mucosal lesions of AIDS-KS are highly varied in configuration, being oval, elongated, fusiform, or irregular in shape.<sup>5</sup>

The epidemiology of KS in the AIDS population strongly suggested an infectious agent. In 1994, a new human herpes virus (HHV) was found to be present in almost 100% of KS lesions. It is now believed that HHV-8 is necessary, but not sufficient, to cause KS, and that other factors such as immunosuppression play a major role.<sup>6</sup>

### 5. What is the differential diagnosis of this condition?

A number of other vascular tumors may mimic KS clinically and/or histologically. Such conditions range from the common pyogenic granuloma to the rare hemangiopericytoma. Of particular interest are the other vascular lesions of infectious (i.e. bacterial) etiology such as bacillary angiomatosis and verruca peruana; proper diagnosis usually requires correlation of the clinical and histologic findings.<sup>7</sup>

### 6. How should this condition be treated?

Current treatment for classical localized Kaposi's sarcoma is based on radiation therapy, while chemotherapy has only a marginal role. Chemotherapy is the treatment of choice in AIDS patients with widespread cutaneous, visceral or progressive disease.<sup>8</sup> Other treatment modalities such as simple excision, cryotherapy, laser therapy and intralesional therapy are used for localized lesions.<sup>9</sup> These modalities cannot be used in patients with widely involved skin areas, whereas therapy with interferon alpha, human chronic gonadotropin and pegylated-liposomal doxorubicin are also effective in the treatment of disseminated KS.<sup>10</sup> However, vinblastine is inexpensive and produces the same result, and excellent responses. Vinblastine produces a response rate of 90% in cutaneous disseminated KS.<sup>11</sup>

### Discussion

In 1872, Moriz Kaposi described five elderly patients with idiopathic multiple pigmented sarcoma, later designated Kaposi's sarcoma. During the following century, this unusual tumor was also described in isolated endemic African populations and immuno-suppressed organ transplant recipients. In 1981, Kaposi's sarcoma emerged from relative obscurity as a predominant feature of the AIDS epidemic. Four clinical types are recognized. The classic or chronic form usually affects elderly men of Eastern European or Mediterranean origin and usually involves the lower limbs, with gradual proximal progression. The lesions present as violaceous or brown-red macules, plaques or nodules. A second, more rapidly progressive African variety has been recognized, in which lymph node involvement is predominant and skin lesions are infrequent. A third form of Kaposi's Sarcoma may develop months to years after renal transplantation, the extent of the process correlating with the loss of cellular immunity. The fourth form has been recognized in association with the acquired immunodeficiency syndrome (AIDS). The lesions in this last type differ in their color (brighter red) and location (upper trunk and mucosa).

Kaposi sarcoma is a malignant tumor of lymphatic endothelial cell origin. The behav-

ior of Kaposi sarcoma is variable and depends on a number of factors, including the immunologic competence of the host. The classical form is slowly progressive, while the other forms are more rapidly progressive. Human herpes virus 8 (HHV-8) was found in tissue of patient with KS irrespective of clinical type. Detection of HHV-8 in HIV-infected individuals who do not have KS is predictive of the development of KS, usually within 2 to 4 years.

Kaposi's sarcoma is associated with an increased risk of developing second malignancies, such as malignant lymphoma (Hodgkin's disease, T-cell lymphoma, non-Hodgkin's lymphoma), leukemia and myeloma. The risk of lymphoreticular malignancy is about 20 times greater in KS patients than in the normal population.

Owing to the multicentric nature of this tumor, radiation or chemotherapy rather than surgical excision is indicated. All types of KS are radiosensitive. Intralesional injection of cytotoxic agents such as vincristine is helpful for symptomatic treatment of the cutaneous lesions.

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