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Case Report

Kaposi's sarcoma after liver transplantation: case report

Sarcoma de Kaposi pós-transplante hepático: relato de caso

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ABSTRACT: *Introduction:* Kaposi's Sarcoma is a multicentric malignant neoplasm characterized by the development of purple tumors, which can be seen on the skin and subcutaneous tissue and on viscera. The objective of this study was to report a case of Kaposi's Sarcoma after liver transplantation, considering the rarity of this event. *Method:* The research instrument used to conduct this report was the case study, with collection of information from the patient's physical record. *Case report:* A 28-year-old man with a history of using Tacrolimus for three years due to liver transplantation, presented abdominal pain associated with diarrhea, and was diagnosed with Kaposi's Sarcomi through histopathological examination of intestinal polyp and referred for chemotherapy treatment. *Final considerations:* Patients who were submitted to solid organ transplants and treated with immunodepressive medications should have any new symptoms carefully investigated to allow an early diagnosis of neoplasia.

Keywords: Sarcoma; Immunosuppression; Liver transplantation; Case report.

RESUMO*: Introdução:* O Sarcoma de Kaposi constitui uma neoplasia maligna multicêntrica caracterizada pelo desenvolvimento de tumores vinhosos, os quais podem ser observados tanto na pele e no tecido subcutâneo como em vísceras. O objetivo deste estudo foi relatar um caso de Sarcoma de Kaposi após transplante hepático, pela raridade da ocorrência desse evento. *Método:* O instrumento de investigação usado para a condução deste relato foi o estudo de caso, com a coleta das informações em prontuário físico do paciente. *Relato do caso:* Homem de 28 anos, com história de uso de Tacrolimus há três anos devido a transplante hepático, apresentando dor abdominal associada a diarreia, diagnosticado por meio de histopatológico de pólipo intestinal com Sarcoma de Kaposi, encaminhado para tratamento quimioterápico. *Considerações finais:* Pacientes receptores de transplantes de órgãos sólidos que recebem medicações imunodepressoras devem ter novos sintomas cuidadosamente investigados, para possibilitar diagnóstico neoplásico precoce.

Palavras-chave: Sarcoma; Imunossupressão; Transplante de fígado; Relato de caso.

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INTRODUCTION

Kaposi's sarcoma was first described in 1872 by dermatologist Moritz Kaposi as "idiopathic multiple hyperpigmented sarcoma"[1]. This disease is nowadays defined as a multicentric angioproliferative neoplasm that affects mainly the skin, but may also affect internal organs such as lungs, liver and intestine[2]. It also causes tumors in the subcutaneous tissue or in the mucous membranes, with the appearence of raised macules or purple, brown, or red nodules, sometimes painful[3].

The annual incidence of Kaposi's sarcoma is between 0.02 and 0.06% of all malignant tumors. Men are more affected than women, in a ratio of 15 men to one woman[1].

The literature describes four subtypes of Kaposi's Sarcoma based on their clinical and epidemiological characteristics: a) *classic or sporadic* – occurs more commonly in older men of Mediterranean or Jewish ancestry, affects mostly the lower limbs and has a chronic and indolent course; b) *African or endemic* – more aggressive lymphadenopathic form, which occurs mainly in children; c) *iatrogenic* – related to pharmacological immunosuppression mainly after organ transplants; d) *epidemic or AIDS-related* – highly aggressive, seen most often in young men with the human immunodeficiency virus (HIV)[4-5].

In addition, iatrogenic Kaposi's sarcoma has been occurring in patients using drugs such as Cyclosporine, Cyclophosphamide, Corticoids and Azathioprine, as these substances cause immunosuppression, and the neoplasm may regress after suspension of drug therapy[3]. The incidence of Kaposi's sarcoma in transplant patients ranges from 2% to 3.5%, a rate much higher than that presented by the general population[6]. However, this neoplasm rarely occurs after liver transplantation[7], being detected more frequently in patients undergoing kidney transplantation[8].

The pathogenesis of Kaposi's sarcoma is not fully understood. Immunological and environmental factors seem to play a role in the aetiology of the disease in people with genetic predisposition[2]. It is important to emphasize that the human herpes virus type 8 (HHV-8) is clearly associated with the four types of Kaposi's Sarcoma, however, it has not been demonstrated that HHV-8 alone is sufficient for the development of the disease[3]. The virus transmission route is not clear, but it is frequently detected in the saliva and semen of patients infected with Kaposi's Sarcoma[1].

As for the pathophysiology of sarcoma, it initiates with an immune dysregulation characterized by the "CD8+ T cell activation and the production of Th1-type cytokines that induce a generalised activation of endothelial cells leading to adhesion and tissue extravasation of lympho-monocytes, spindle cell formation and angiogenesis"[9]. This process is triggered or enhanced by the presence of herpes virus type 8, which is, in turn, reactivated by these cytokines[9].

Regarding iatrogenic Kaposi's sarcoma, it is important to mention that, despite the occurrence of this neoplasm in up to 3.5% of patients undergoing solid organ transplants, it is rare in liver transplant recipients, occurring in about two out of every 1000 transplants of that organ[7]. Thus, this study is relevant as it aims to report a clinical case of a patient diagnosed with Kaposi's Sarcoma after pharmacological immunosuppression due to liver transplantation.

METHOD

The research instrument used to conduct this report was the case study, a method widely adopted in the medical field, as it allows a detailed and dynamic analysis of a given disease in a person, contributing to medical teaching, among other aspects[10-11]. The present study has a descriptive, narrative and reflective design, and is derived from professional practice.

Data collection was carried out through the analysis of the patient's medical record at the *Hospital Universitário Oswaldo Cruz, Recife, Pernambuco*, Brazil. As for the ethical aspects involved in study, those recommended by Resolution 466/2012 of CNS/MS/BRAZIL and its complementary resolutions were followed[12], such as, above all, the guarantee of the patient's anonymity, the confidentiality of the information and the patient's autonomy to participate in the study, guaranteed by the Informed Consent Form (Annex).

In this case report, the discussion is supported by Yoshida's recommendations[13]. In the author's understanding, a study should emphasize the uniqueness of the report, the accuracy of the diagnosis and its validity in comparison with the data in the literature.

CASE REPORT

A 28-year-old male patient with diagnosed with primary sclerosing cholangitis in 2014 underwent a liver transplant in October 2015. Due to the occurrence of hepatic artery thrombosis, a second liver transplant was performed in the same year. The immunosuppressive therapy used after transplantation consisted of Tacrolimus 9mg a day and Mycophenolate sodium 360mg at night. Approximately three years after the second transplant, the patient sought medical care at the *Hospital Universitário Oswaldo Cruz, Recife, Pernambuco*, reporting diffuse abdominal pain, watery diarrhea, cough with white sputum and febrile episodes for one month, and was admitted to a clinical ward for investigation of the condition. The patient reported two episodes of blood in stool, in addition to a weight loss of about 4.5 kg in this period.

Physical examination showed absent breath sounds in the auscultation of the right hemithorax. A chest Xray was performed and showed a massive pleural effusion on the right side. Chest and abdomen tomography were conducted and presented the following results: significant pleural effusion on the right side, determining partial collapse of the adjacent lung, mediastinal shift to the left and moderate ascites. After confirmation of pleural effusion on chest tomography, chest drainage was performed, with the output of 1300 ml of viscous serous fluid with discrete lumps. Subsequently, pleural biopsy and closed pleural drainage were performed. During these procedures, the following aspects were observed: elimination of a moderate amount of pleural fluid (empyema), smooth pleura without thickening or nodules, pericardial nodules (also biopsied) and free lung with no alterations. Results of biopsies of the pleura and pericardial nodules demonstrated a chronic inflammatory process without signs of malignancy. To further elucidate the causes of ascites, diagnostic paracentesis was also performed and showed cloudy and purulent ascitic fluid, with cellularity of 1600 cells/mm³ and predominance of mononuclear cells (80%), with negative culture.

To adjust the dose and obtain maximum immunosuppression and minimal toxicity, the serum concentration of Tacrolimus in the patient was measured, resulting in 30 mcg/L. Due to the high value, the daily dosage of the drug was reduced to 7mg per day.

During hospitalization, the diagnostic hypothesis of pulmonary and intestinal tuberculosis was considered due to pulmonary involvement and gastrointestinal symptoms associated with immunosuppression, which led to the suspension of mycophenolate sodium. However, this hypothesis was discarded after the following results: 0mm PPD, negative bacilloscopy, AFB and ADA in pleural fluid analysis, and negative genexpert in a fragment of the pericardial nodule.

Therefore, the etiological investigation of the patient's clinical condition was expanded with other laboratory tests, such as serum galactomannan antigen test (negative) and serology for cytomegalovirus and HIV (non-reactive).

The in-depth investigation of the watery diarrhea presented by the patient through colonoscopy (without reaching the ileum) allowed the diagnosis of severe ulcerative colitis (Mayo III), pseudopolyps and subpedunculated polyp (Yamada II) in the transverse colon. In a subsequent colonoscopy procedure, polypectomy with clipping in the proximal ascending colon (Yamada III) was performed and sent for histopathological examination. This second examination also showed pancolitis, with signs of chronicity (suggestive of ulcerative colitis), for which therapy with Mesalazine 4.8g per day was prescribed.

Finally, the anatomopathological analysis of the intestinal polyp, including immunohistochemical examination of the sample (Figures 1-3), confirmed the presence of Kaposi's Sarcoma (in the tumor phase). It is worth noting that the detection of herpes virus type 8, strongly associated with the presence of Kaposi's Sarcoma, could not be performed, as the health service in which the patient was admitted did not offer the necessary resources for this research.

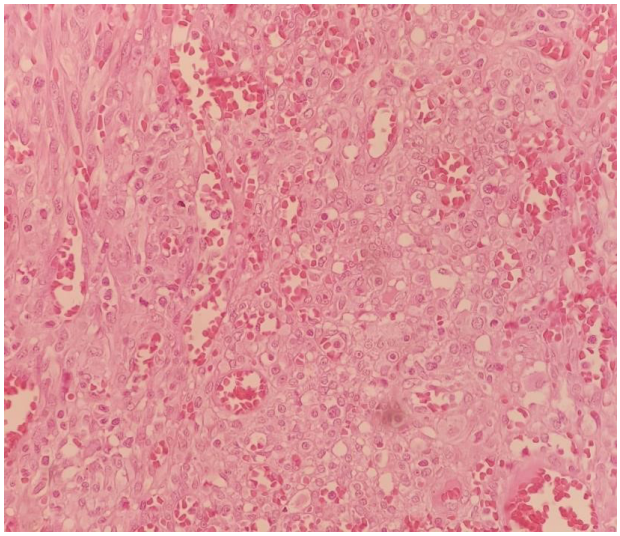

Figure 1: Kaposi's sarcoma malignant cells (H&E stain, 400x magnification)

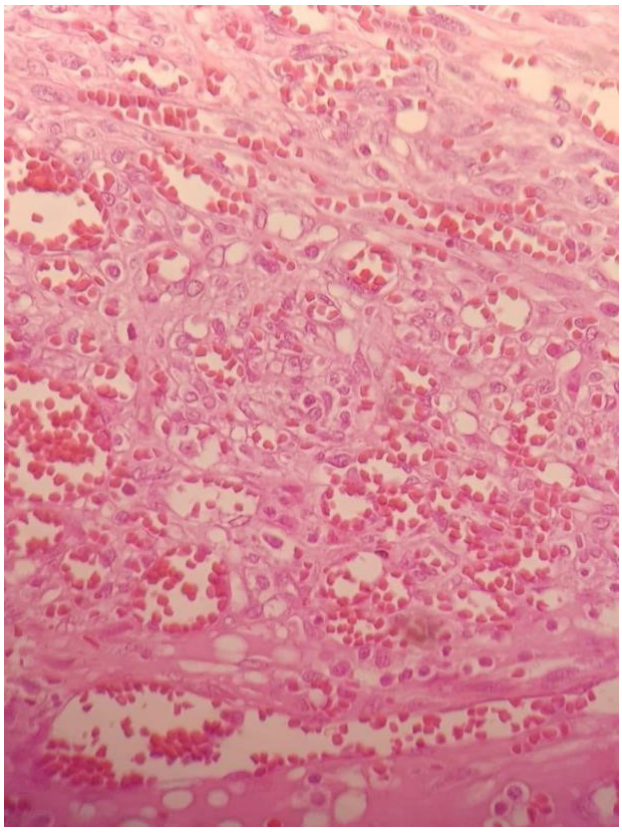

Figure 2: Proliferation of cells of vascular origin (H&E stain, 400x magnification)

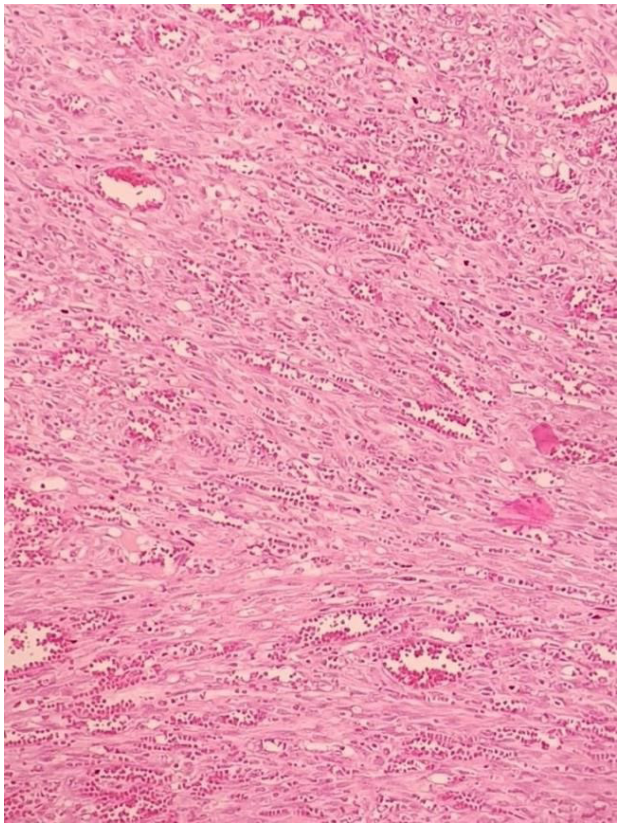

Figure 3: Kaposi's sarcoma malignant cells (H&E stain, 100x magnification)

The patient's diagnosis of Kaposi's sarcoma was attributed to the immunosuppression therapy after liver transplantation. Once the diagnosis was concluded, Tacrolimus was reduced to 6mg a day and infection prophylaxis was started with the use of Sulfamethoxazole 400mg a day and Trimethoprim 80mg a day. Systemic involvement of Kaposi's sarcoma was also confirmed by a left axillary lymph node biopsy. The patient was then referred to the Clinical Oncology team of the health service to start chemotherapy treatment.

DISCUSSION

The origin of Kaposi's sarcoma remains uncertain, but it is known that infectious, genetic, social, immunological and endocrine factors influence the pathogenesis of the disease[4]. As for the clinical condition, records indicate that, initially, the tumor usually generates violaceous skin lesions, which can manifest as macules, plaques, papules or nodules. Oral, lymph node and visceral symptoms may also occur[3], for example, in the respiratory and gastrointestinal tracts.

The clinical course of Kaposi's sarcoma is strongly associated with the degree of organ involvement. Patients with mucocutaneous lesions have a more indolent disease course and often respond to the reduction of immunosuppressive drugs. Conversely, patients with visceral involvement, like the one presented in this case report, experience a more severe form of the disease and a greater chance of death[6]. This is confirmed by the reports of a 50% tumor remission rate in patients with lesions limited to the skin with the reduction of immunosupressive therapy, while patients with visceral involvement have only a 20% remission rate [6].

The first iatrogenic Kaposi's sarcoma was described in 1978 and occurred in a patient who had had a kidney transplant and was on immunosupressive therapy (chronic corticosteroids and systemic chemotherapy)[2]. Among the clinical aspects of this iatrogenic form, integumentary manifestations are frequent, while visceral manifestations appear in approximately 25% of cases[3].

In the present case, the intestine was the most affected organ. It is worth noting that lesions in the gastrointestinal tract can develop even in the absence of skin lesions, and gastrointestinal involvement is more likely in cases of severe immunosuppression at the time of diagnosis and longer duration of the disease. Gastrointestinal Kaposi's sarcoma's lesions can cause abdominal discomfort, pain, bleeding and diarrhea[3], symptoms presented by the patient analyzed in this case.

Immunosuppression associated with the use of Cyclosporine and Tacrolimus (also called FK-506) is considered in some reports as a risk factor for Kaposi's sarcoma[7]. The mean time for the onset of the neoplasm after the start of pharmacological immunosuppression is one year and four months[3]. It is worth mentioning that the patient involved in this study had been using Tacrolimus for three years prior to the diagnosis, which may be an important causal factor for the development of the tumor.

The drug Tacrolimus is derived from the fungus *Streptomyces tsukubaensis* and is 10 to 100 times more potent than Cyclosporine, with 37 times less nephrotoxicity[4]. As for the risk of tumor development associated with the use of these drugs, there seems to be no difference between the two.

A study involving 1000 patients who received liver transplantation and were treated with Tacrolimus found that 82 developed de novo nonlymphoid malignancies, with only two cases of Kaposi's sarcoma. Thus, the authors concluded that these patients did not have a higher risk of developing nonlymphoid tumors when compared to patients treated with Cyclosporine[14].

In the diagnostic process of Kaposi's sarcoma, the immunohistochemical evidence of herpes vírus type 8, which is associated with all forms of neoplasia, is of paramount importance. There is evidence that, in transplant patients, the transmission of herpes virus type 8 occurs from the transplanted organ, which contaminates the recipient[4]. As mentioned, in the case under study, it was not possible to

research the infection by this virus, which was a limitation for the analysis.

Despite the existence of different types of Kaposi's sarcoma with different symptoms and clinical courses, their histopathology is essentially the same[15] and is the basis for the definitive diagnosis of Sarcoma. In the histological analysis, it is possible to find an increase in spindle cells, which may present nuclear pleomorphism, and an increase in vascular structures, with a predominant presence of endothelial cells. Extravasation of erythrocytes and hemosiderin-laden macrophages is also very frequently observed. When Kaposi's sarcoma is already in a late stage, granulation tissue with diffuse and infiltrative chronic inflammation may be seen, in addition to excess capillaries[3].

Due to the multifocal character of Kaposi's sarcoma, the classification into stages is difficult, as there is no universally accepted staging system. In the case studied, the disease was in the disseminated form, due to involvement of the left axillary lymph node (confirmed by biopsy). Kaposi's sarcoma lymphadenopathy is understood as a form of localized nodular sarcoma[3].

Due to the heterogeneity in the manifestation of the tumor, there are no standard therapeutic protocols[2]. The treatment is usually based on the extension of the tumor and the patient's immune status and includes the use of radiotherapy, surgical excision and chemotherapy in clinical practice[3]. In the case of Kaposi's sarcoma in transplant patients, there are no therapeutic protocols that attack the tumor while also protecting the graft[16].

Especially in cases of iatrogenic Kaposi's sarcoma, when the use of corticosteroids and cytotoxic drugs is reduced or interrupted, partial or total remission of the sarcoma may occur[3]. The level of drug reduction depends on the existing lesions and the risk of death from the disease[16]. When possible, these medications should be reviewed before starting cancer treatment, as in the case under study, in which the daily dose of Tacrolimus used by the patient was reduced before the chemotherapy sessions.

FINAL CONSIDERATIONS

The study demonstrates that Kaposi's sarcoma should always be considered in the case of mucocutaneous or visceral lesions in patients with immunosuppression, whether or not linked to HIV. Solid organ transplant recipients on immunosuppressive therapy should have any new symptoms carefully investigated.

Broad knowledge about the possible clinical manifestations of Kaposi's sarcoma, whether cutaneous or extracutaneous, will lead to an early diagnosis of the disease and, consequently, to a more effective therapeutic process. From this perspective, the case studied contributes to clinical research in other similar situations.

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