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Original Article

Iatrogenic Kaposi's Sarcoma: a Retrospective Cohort Study in an Italian Tertiary Care Centre

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Abstract

Aims: Kaposi's sarcoma (KS) is a lymphoangioproliferative multicentric disorder. Among its four distinct clinical variants, iatrogenic KS (iKS) typically affects patients who have received immunosuppressant regimens for organ transplants, proliferative disorders, or immune-mediated diseases. The aim of the current study was to examine the characteristics of a cohort of patients with iKS, evaluating the differences in terms of epidemiological and clinical features, management and outcomes between organ transplant recipients (OTR) and patients immunosuppressed for other medical conditions.

Materials and methods: This retrospective study included, out of 1389 KS patients, 143 patients suffering from iKS being followed in an Italian tertiary care centre from November 1995 to December 2016. Demographic data, clinical features, previous immunosuppressive therapies, management, and outcomes were recorded for each patient.

Results: We detected iKS in 10.3% of the analysed KS population. The mean age was 71.9 years in non-OTR versus 51.4 years in OTR ($P = 0.04$). Staging at diagnosis showed a more severe disease in non-OTR than in OTR, with stage IA observed in 33.3% of OTR versus 11.8% of non-OTR ($P < 0.001$) and stage IVB in 29.1% of non-OTR versus 12.1% of OTR ($P = 0.001$). Corticosteroids represented the most frequent immunosuppressive drugs at diagnosis in both groups, in conjunction with cyclosporine A in OTR. Immunosuppressant reduction or withdrawal was carried out in 93.9% of OTR versus 63.6% of non-OTR ($P < 0.001$).

Conclusions: As corticosteroids and cyclosporine A are the most common iKS-inducing drugs, their reduction or withdrawal, wherever possible, is needed. Differences in disease severity at presentation between OTR and non-OTR may interfere with the choice of management strategy and the consequent outcome.

Key words: Corticosteroids; iatrogenic; Kaposi's sarcoma; organ transplant

Introduction

Kaposi's sarcoma (KS) is a rare lymphoangioproliferative disease associated with human herpes virus 8 (HHV8). Since 1994, when Chang *et al.* [1] identified HHV8, it has been shown that the virus is necessary, but not sufficient, for the development of KS. Indeed, further factors (genetic, immunological and environmental) are required.

Four clinical variants have been distinguished: classic KS, endemic KS, HIV-related KS and iatrogenic KS (iKS), the latter occurring in patients undergoing immunosuppressive treatments for organ transplant, malignant processes or immune-mediated diseases [2]. Indeed, during the 1960s, an increased incidence of KS was found in the USA and Canada in allograft recipients, as well as in other patients on long-term immunosuppressive therapy [3]. The incidence of KS is between 100 and 500 times higher in organ transplant recipients (OTR) than in the general population, with variability in different geographical areas [4,5], whereas it is two- to four-fold lower compared with OTR in patients immunosuppressed for other medical conditions [6]. Although several hypotheses have been proposed, the currently most accepted is that immunosuppressants lead to iKS by weakening the immunological surveillance system, reactivating a pre-existent HHV8 infection and giving rise to the proliferative transformation of the infected endothelial cells. Less frequently – and only in some OTR –

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seroconversion may follow the immunosuppression, suggesting infection from the donated organ [7].

Exclusive cutaneous and/or mucosal involvement is usually seen, even though widespread disseminated forms with visceral involvement may be found. Clinical manifestations generally resolve after immunosuppressive drugs are reduced or discontinued, whereas maintaining immunosuppression frequently leads to further disease progression. Prognosis also depends on the severity at presentation [8]. Although several retrospective cohort studies about transplant-related iKS have been conducted [9–12], we observed that only isolated case reports or case series concerning iKS in patients other than OTR were described in the literature. Therefore, to expand our knowledge about epidemiological and clinical features of this KS subtype, we retrospectively characterised iKS patients undergoing immunosuppressive regimens for either organ transplant or other medical conditions, seen at a tertiary referral centre for the diagnosis and treatment of KS in northern Italy.

Materials and Methods

Patients and Study Design

We conducted a retrospective analysis of 143 patients with iKS admitted to our outpatient service from November 1995 to December 2016. All data were collected from the computerised database of our department. Inclusion criteria were as follows: (i) histologically confirmed diagnosis of KS; (ii) immunosuppressive treatment before KS onset; (iii) positivity for anti-HHV8 antibodies on blood test. Exclusion criteria included: (i) congenital immunodeficiencies; (ii) positivity for HIV-1 or -2 on the enzyme-linked immunosorbent assay (ELISA) test.

Clinical examinations were carried out during each visit; routine blood analysis, chest radiograph, otolaryngological assessment, oesophagogastroduodenoscopy, abdomen ultrasound scan, faecal occult blood test were carried out during the staging process and repeated if necessary, to exclude visceral KS lesions. A histological examination was carried out on skin or mucous biopsies for each patient. The analysed data included demographic and clinical characteristics for each patient, such as birthplace, gender, age at onset of iKS, underlying disease, KS-related immunosuppressive therapy, latency period between the start of immunosuppression and KS diagnosis, stage of the disease at diagnosis, location and clinical presentation of KS, management strategies and outcome at the last follow-up.

Patients were staged according to the classification proposed by Brambilla *et al.* [13] for classic KS. Outcomes at the last follow-up visit were recorded. Complete remission was defined as the disappearance of all clinical manifestations, including tumour-associated oedema. Partial response was defined as the absence of new lesions (skin, oral or visceral), the absence of worsening of tumour-associated oedema and at least a 50% decrease in the number of all previously existing lesions, or complete flattening of at least 50% of all previously raised lesions, or a 50% decrease in the sum of the products of the largest perpendicular diameters of the macular lesions, or patients with residual tumour-associated oedema who otherwise met the criteria for a complete remission. Partial response had to be maintained for at least 4 weeks. Progressive disease was recorded on the basis of any of the following criteria: an increase of 25% or more in the size of previously existing lesions, the occurrence of new lesions or sites of disease, a change in the features of 25% or more of existing skin or oral lesions from macular to plaque-like or nodular, and the development of new or increasing tumour-associated oedema. Any response that did not meet the criteria for complete remission, partial response or progressive disease was defined as stable disease.

Statistics

The collected data were computerised and statistically analysed using GraphPad Prism version 6.0 (GraphPad Software, Inc., San Diego, CA, USA).

Categorical variables were shown as mean and standard deviation and continuous variables as absolute and relative frequencies. The qualitative data were evaluated using Fisher's exact test. The significance level was considered at P-value < 0.05.

Results

Demographic Data

One hundred and forty-three of 1389 KS patients showed an iKS that met the inclusion criteria and were eligible for the study. Thirty-three patients were OTR, whereas 110 patients had received immunosuppressive treatments for other reasons. The patient characteristics are summarised in Table 1.

Among OTR, 48.5% came from southern Italy and insular regions, 48.5% from northern Italy and one patient from Egypt. Among non-OTR, 59.1% came from northern Italy, 1.8% from central Italy, 37.3% from southern Italy and insular regions, one patient from Switzerland, one patient from Sub-Saharan Africa and one patient from Great Britain.

Clinical Features

The most common skin and/or mucosal lesions were nodules both in non-OTR and in OTR (67.3% and 66.7%, respectively). The most common skin and/or mucosal localisation was represented by lower limbs in both groups. Visceral involvement was observed in seven (6.4%) non-OTR and three (9.1%) OTR. Five patients with visceral involvement in the non-OTR group had localisation of the disease in the gastrointestinal tract, one in the liver and one in lymph nodes, whereas in OTR, lymph nodes were involved in two cases and the lung in one case. The most common complication in both non-OTR and OTR was lymphoedema (88.6% and 100% of the complicated cases, respectively). In non-OTR lymphorrhoea, ulceration or functional

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