Virchows Arch (1999) 435:612–615

CASE REPORT

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Kaposi's sarcoma following malignant mesothelioma

Received: 12 April 1999 / Accepted: 24 June 1999

Abstract We report the unusual occurrence of Kaposi's sarcoma following asbestos-related malignant mesothelioma, in a human deficiency virus (HIV)-negative Italian man. Seropositivity to human herpes virus 8 (HHV8) was documented at the time of mesothelioma diagnosis and preceded the onset of Kaposi' sarcoma with a time lapse of 13 months. HHV8 DNA was detected by polymerase chain reaction in lesional Kaposi's sarcoma but not within mesothelioma. By immunostaining, mesothelioma cells expressed interleukin-6 and platelet-derived growth factor, which are important for survival of Kaposi's sarcoma cells. Besides the possibility of a casual association, we hypothesize that mesothelioma-linked factors may have contributed to the development of Kaposi'sarcoma in the presence of HHV8 infection.

Key words Kaposi sarcoma · Mesothelioma · Interleukin-6 · Platelet-derived growth factor · Herpes virus · Kaposi-sarcoma associated

Introduction

Kaposi's sarcoma (KS) is an angioproliferative process of uncertain and multifactorial pathogenesis. KS-associated herpes virus (also known as human herpes virus 8/HHV8) is the candidate infectious cofactor of KS, because HHV8 DNA sequences are found in all forms of KS [11]. In addition, seroepidemiological studies show that the HHV8 seroprevalence correlates with the incidence of KS [5, 8, 22]. KS is influenced by cytokines [4] and is strongly associated with reduced immune competency. Altered host immunity is evident in acquired immunodeficiency syndrome (AIDS)-related KS and post-transplant KS, but it is also true of classic/endemic cases [17]. Classic KS may occur as second primary neoplasm following hematopoietic or nonhematopoietic malignancy [3, 6]. It is conceivable that HHV8 is present in HHV8-seropositive individuals in latent form, and it may reactivate when other predisposing factors are present.

We observed an HHV8-seropositive/HIV-seronegative Italian patient who developed classic KS 13 months after the diagnosis of asbestos-related malignant mesothelioma (MM) of the pleura.

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Clinical history

A 63-year-old man without antibodies against human immunodeficiency virus (HIV–Ab) and hepatitis C virus (HCV–Ab) and who was hepatitis B surface antigen seronegative (HBs–Ag) (birthplace: Campania, southern Italy) presented with recurrent pleural effusion. He had a history of asbestos exposure. Cytohistological findings in conjunction with immunophenotype were consistent with a diagnosis of MM (August 1995). Treatment consisted of talc poudrage of the pleural cavity followed by chemotherapy with cisplatin. Thirteen months after the diagnosis of MM (September 1996), the patient developed a nodular KS lesion of the right foot that recurred 4 months later (January 1997). He died at home of respiratory failure due to his MM (June 1997). No autopsy was performed.

Materials and methods

The pleural-fluid sample was received fresh after thoracentesis and the cell pellet was examined by Papanicolaou and May-Grünwald-Giemsa staining. Cells were cryopreserved in dimethyl sulfoxide (DMSO)/fetal calf serum. Pleural and skin biopsies were fixed in 10% buffered formalin and routinely embedded in paraffin. Immunostaining was performed on paraffin sections and/or acetone-fixed cytospins, using a labeled streptavidin biotin

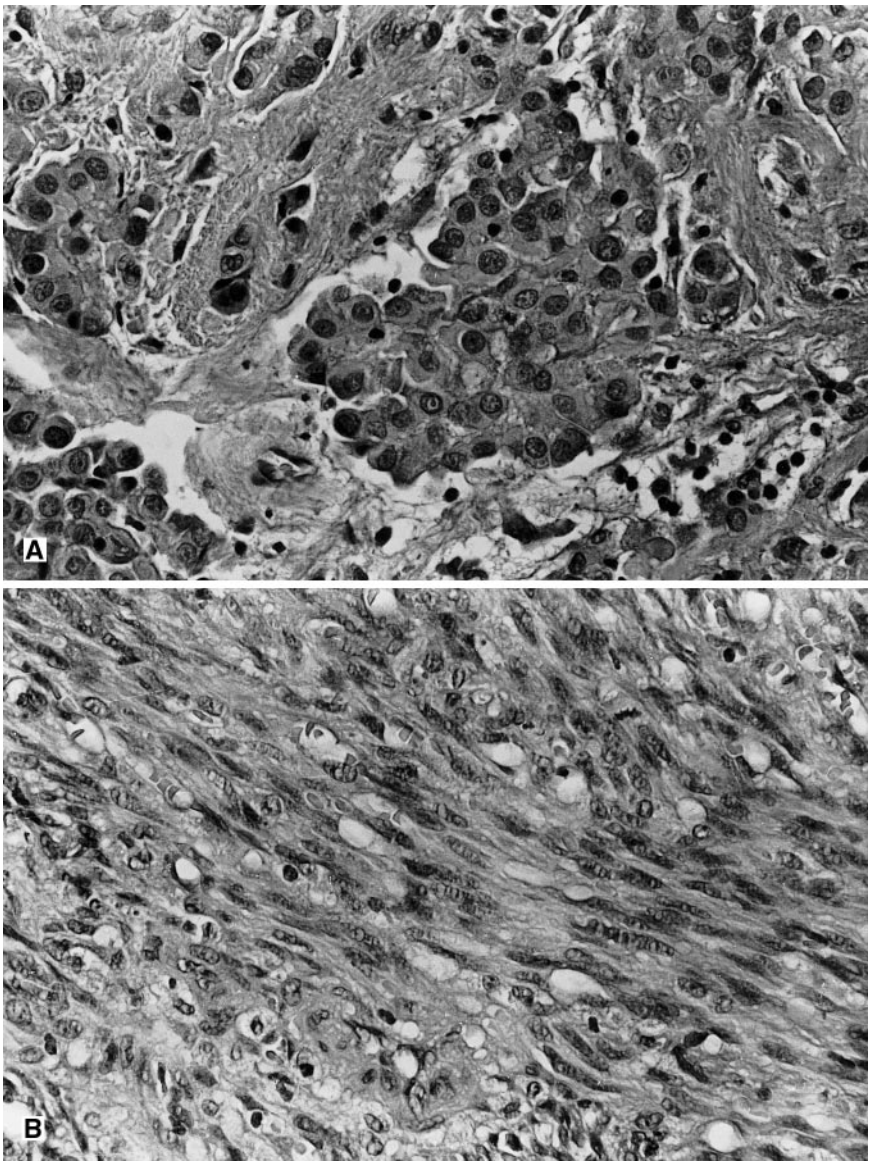

Fig. 1 Histology shows (**A**) malignant mesothelioma of epithelial type in the pleural biopsy and (**B**) Kaposi's sarcoma in the skin biopsy. (hematoxylin and eosin, original magnification ×200)

(LSAB) method and the commercially available polyclonal and monoclonal antibodies against carcinoembryonic antigen (CEA, 1:50), Ber-EP4 (1:100), epithelial membrane antigen (EMA, 1:25), cytokeratin (CKMNF116, 1:50), HBME-1 (anti-human mesothelial cells, 1:50), thrombomodulin (TM, 1:50), calretinin (1:750), CD34 (QBEnd/10, 1:20), platelet-derived growth factor (PDGF-BB, 1:25) and human interleukin-6 (IL-6, 1:20). Reagents were supplied by DAKO (Glostrup, Denmark), Genzyme (Mass.), Chemicon (Calif.), Signet (Mass.) and Becton Dickinson (Calif.).

Genomic DNA was extracted from cryopreserved cell suspensions of MM and from paraffin-embedded sections of KS. Single step (non-nested) polymerase chain reaction (PCR) to detect HHV8 DNA sequences was performed using the PCR conditions and primer set for KS330233, as reported elsewhere [1, 11]. PCR experiments for HHV8 detection included the co-amplification of DNA extracted from a previously characterized HHV8-positive KS biopsy as positive control. In addition, in order to assess the integrity of DNA, we co-amplified a 215-bp fragment of the non-coding 5' region of the Bcl-6 gene using the primers 5'-AGGAAGGAGGGGAATTAG-3' and 5'-AAGCAGTTTGCAAGCGAG-3'.

A serum sample that had been collected on the day of thoracentesis (at that time the patient was free of KS) was tested by an indirect immunofluorescent assay to detect antibodies to HHV8 lytic-associated antigens [8].

Pathologic, molecular and serologic findings

Effusion cytology revealed many cell aggregates with a berry-like contour, characteristic of MM. Histology of the pleural biopsies showed infiltrating tubulopapillary structures and solid sheets of tumor cells consistent with epithelial MM (Fig. 1A). Cutaneous lesions showed the characteristic changes of the nodular stage of KS: spindle-shaped cells arranged in interweaving fascicles, vascular channels and ectatic lymphatic-like channels, extravasated red blood cells and a few lymphocytes and monocytes/macrophages. (Fig. 1B). Negative staining for CEA and Ber-EP4 coupled with positive staining for EMA, cytokeratin, HBME-1, TM and calretinin were seen in mesothelioma cells. Almost all mesotheliomat-

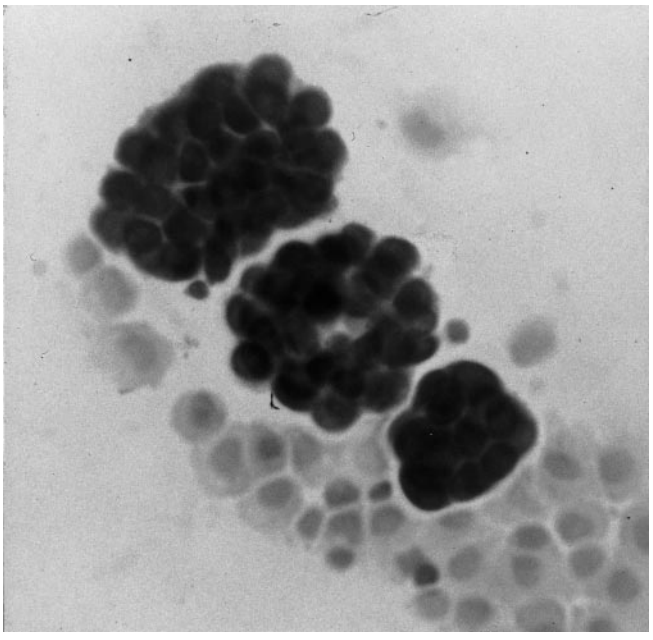

Fig. 2 Immunostainig for human interleukin-6 reveals cytoplasmic staining in mesotheliomatous cells derived from pleural effusion; surrounding macrophages are negative (original magnification ×500)

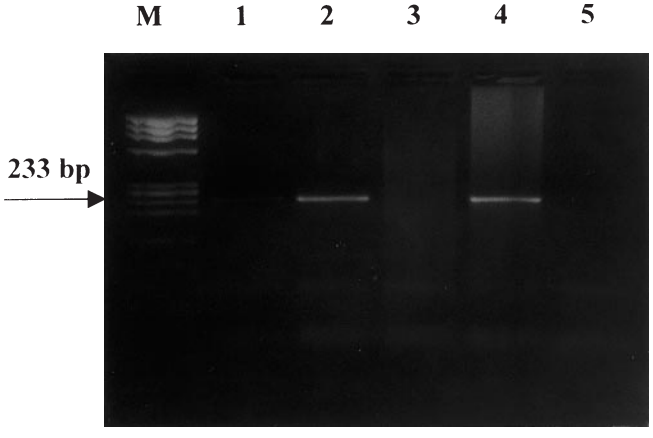

Fig. 3 Results of polymerase chain reaction amplification of $KS330_{233}$ sequences in DNAs obtained from different patients' samples. *Lane 1* DNA extracted from the KS biopsy obtained at relapse; *lane 2* DNA extracted from the KS biopsy at presentation; *lane 3* DNA obtained from the malignant mesothelioma (*MM*) biopsy; *lane 4* positive control (DNA from a classical KS biopsy); *lane 5* negative control (all reagents plus water). *M* molecular weight markers; *arrow* indicates the specific 233-bp amplification band corresponding to $KS330_{233}$ sequences

ous cells were positive for PDGF-BB and IL-6 (Fig. 2). Spindle cells of KS lesions stained positive for CD34.

HHV8 DNA sequences were detected in both KS lesions (at first presentation and recurrence) but not in the MM specimen (Fig. 3). The serum sample resulted HHV8 anti-lytic-positive at high titers (1:640).

Discussion

This is the first fully documented case of classic HHV8-positive KS following pleural MM. Previously, only a report was made of MM associated with KS (article in Czech; no abstract available) [16]. Although a casual relationship between MM and KS cannot be derived from the present single observation, we speculate that this unusual association appears to be more than coincidental. In our patient, KS developed in the context of HHV8 infection that is the essential predisposing factor for KS, but MM-linked co-factors may have contributed to the development of KS.

Seropositivity to HHV8 (demonstration of prior HHV8 exposure) was documented at the time of MM diagnosis and preceded the onset of KS, thus confirming HHV8 infection as high risk factor for KS [8].

The finding of HHV8 DNA in lesional KS but not within MM cells excludes a common etiology, which is in keeping with previous observation [1]. On the other hand, latent HHV8 infection may have reactivated during MM-development/progression. In fact, the first KS lesion appeared about 1 year after MM diagnosis. By analogy, the occurrence of KS as a complication of solid organ transplantation is reported after a mean delay of 16 months [5]. KS, besides being linked to HHV8 and immunosuppression, may initiate and be promoted by multiple factors, including inflammatory cytokines and growth factors [4, 10, 20]. Immunological functions are known to be altered in MM [9]. Moreover, this tumor has been shown to secrete several growth factors and cytokines, including PDGF [7] and IL-6 [12, 18], which leak into the systemic circulation and are important for survival of KS cells [13]. Interestingly, our MM case expressed both PDGF and IL-6. Thus, MM-related immunodysregulation coupled with IL-6- and PDGF-paracrine stimulation of HHV8 infected cells might have contributed to development of KS, in addition to autocrine stimulation (HHV8 itself encodes a functionally active homolog of IL-6) [14]. Although we cannot formally prove whether these factors were operational in the present case, we consider the hypothesis that MM could have played a role in triggering KS. A cisplatin treatment-related risk factor (the only therapeutic drug applied before KS development) is unlikely [15].

Patients with neoplastic diseases who are HHV8-seropositive might have predisposing co-factors for developing classic KS (or other HHV8-associated diseases). A recent study has investigated the incidence and estimated the risk of developing classic KS as a second primary neoplasm [6] and reported an excess of secondary KS following certain cancers. In addition, multicentric Castleman's disease [21] and body-cavity-based lymphoma [2, 19] have been described following primary cancers. This is possibly relevant in populations at risk, notably in individuals of southern European ancestry and southern Italy, geographical areas at high incidence of classic KS and HHV8 seroprevalence [5, 22].

Acknowledgements This work was supported by grants from the Ministero del Lavoro e della Previdenza Sociale (n.761).

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