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CASE REPORT

Very Rare Mediastinal Location of Kaposiform Haemangioendothelioma: a Case Report and a Brief Review of the Previously Published Cases

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Abstract

Kaposiform haemangioendothelioma (KHE) is a rare, locally invasive vascular tumour that is commonly associated with the Kasabach-Merritt phenomenon (KMP). A case of a five-month-old female infant admitted for dyspnoea, stridor, and skin haematoma is presented. Computerised tomography of the chest showed a tumour mass occupying mediastinum and most of the left hemithorax, while laboratory analysis revealed a thrombocytopaenia and a consumption coagulopathy. Histology of tumour biopsy was characteristic of KHE with a component of tufted angioma. Corticosteroid treatment initially induced a reduction in tumour size, but progression occurred four weeks later and led to a fatal outcome despite additional chemotherapy. After a literature search, we found only 18 cases of mediastinal KHE published so far, with 21 % fatality rate. In the present case several risk factors for adverse outcome were present: onset of disease in early infancy, a large volume of the tumour, mediastinal location, KMP, and partial response to available therapy.

Key words: kaposiform haemangioendothelioma; Kasabach-Merritt phenomenon; mediastinum; infant.

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Introduction

Childhood tumours represent just over 1 % of all human tumours. They are different from tumours in adolescents and adults regarding histological types, biology, incidence, clinical features, prognosis, and response to treatment. In the era of multimodal anticancer therapy, the majority of malignant tumours in childhood have a favourable prognosis. In contrast, benign tumours at that age may cause death due to their anatomic location and size.[1, 2] In a series of more than 900 benign and malignant soft tissue tumours detected in the first two decades of life, 30 % were of vascular origin.[3] Estimates of the overall prevalence of vascular anomalies range from 6 % to 25 %.[4] The most frequent location is the skin, followed by mucous membranes, deep connective tissue, and internal organs.[1] According to the 2014 update of the International Society for the Study of Vascular Anomalies (ISSVA) Classification, vascular anomalies are divided into two main groups, namely vascular malformations and vascular tumours, which are further classified into benign, locally aggressive (borderline), and malignant.[5]

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Here, a case of kaposiform haemangioendothelioma (KHE), a sporadic, locally aggressive, vascular tumour in a very rare extracutaneous, mediastinal location in a female infant is presented. After adding our case, which is, to the best of our knowledge, the 19th published case of KHE in that location, the clinical-pathological aspects of mediastinal KHE were analysed, with the addition of a brief literature review of the cases published thus far.

Case history

A five-month-old girl presented with stridor and dyspnoea. During a course of treatment for bronchiolitis (including systemic corticosteroids), she developed numerous petechiae and haematomas in the skin. Blood analysis revealed severe thrombocytopaenia and she was referred to our tertiary care paediatric hospital in early 2005. Computerised tomography (CT) of the chest showed a soft tissue tumour mass occupying the mediastinum and most of the left hemithorax, measuring more than 20 cm in its largest diameter (Figure 1A). The tumour extended from the base of the neck to the diaphragm, compressing the mediastinal structures (trachea, oesophagus and aorta) as well as the left main bronchus, causing atelectasis of the left lung which was confirmed by fibre-optic bronchoscopy. Laboratory analysis verified a severe consumption coagulopathy with thrombocytopaenia (14 x 10^9/L), hypofibrinogenaemia (0.42 g/L), and elevated D-dimer levels (11.70 mg/L) which was consistent with Kasabach-Merritt phenomenon (KMP). Severe anaemia was also present (haemoglobin 76 g/L) with schistocytes detected in the peripheral blood smear. After the initial stabilisation of the gas exchange using the

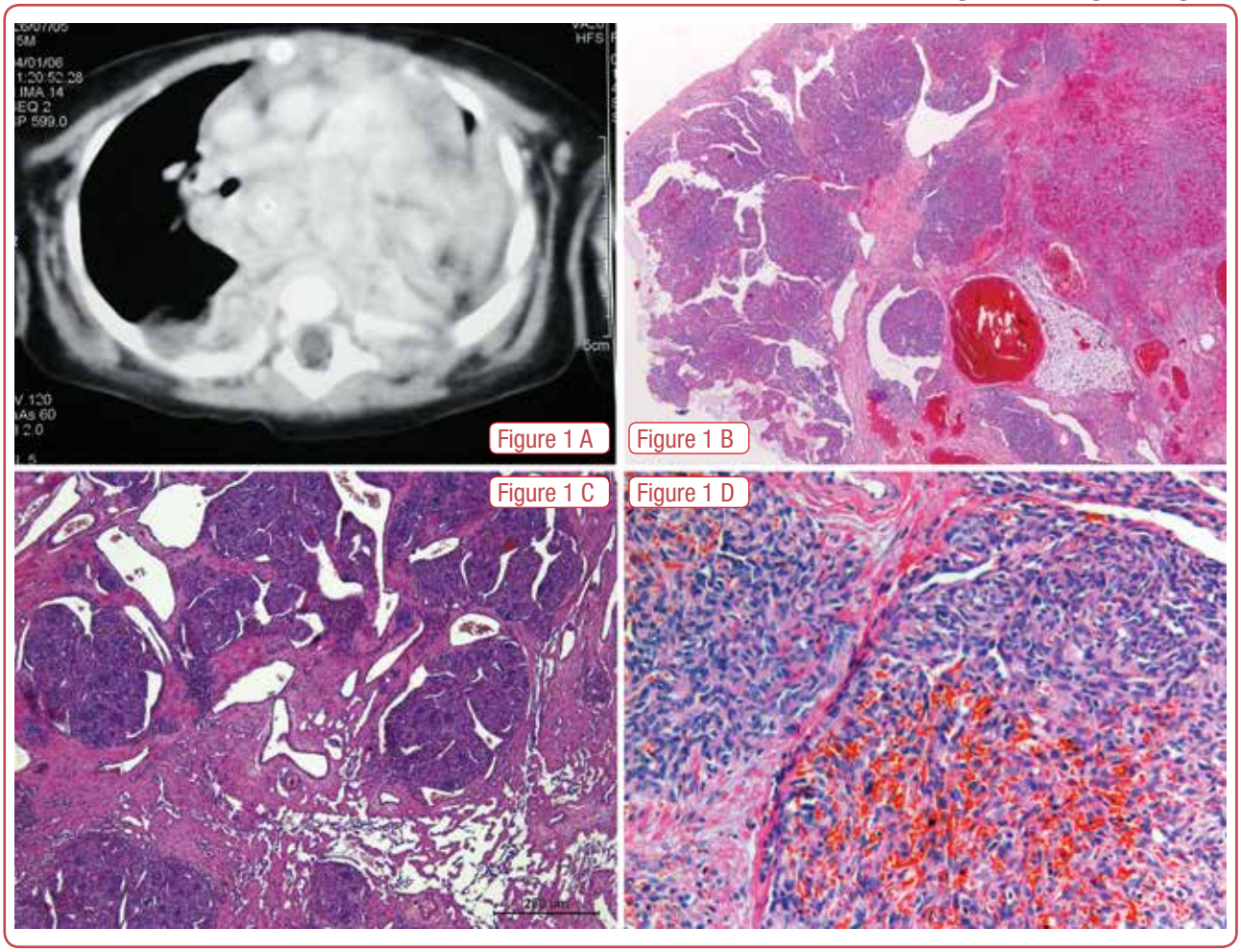

Figure 1A. Contrast-enhanced CT image of the chest showing large, lobulated tumour mass occupying mediastinum and left hemithorax. Figure 1B–D. Microscopic features of kaposiform haemangioendothelioma. B. Infiltrating growth of tumour in nodules with several dilated, blood-filled vascular spaces and a solid, densely cellular, partly haemorrhagic area in the right part of the picture (haematoxylin-eosin, HE, x 25); C. Tumour nodules bulging into the outer crescent-shaped thin-walled vascular spaces typical for tufted angioma, mixed with malformed, thin-walled lymphatic vessels (HE, x 50). D. Densely cellular, spindle-cell tumour component in fascicles interspersed with tiny capillaries and lining slit-like vascular channels filled with erythrocytes (HE, x 400).

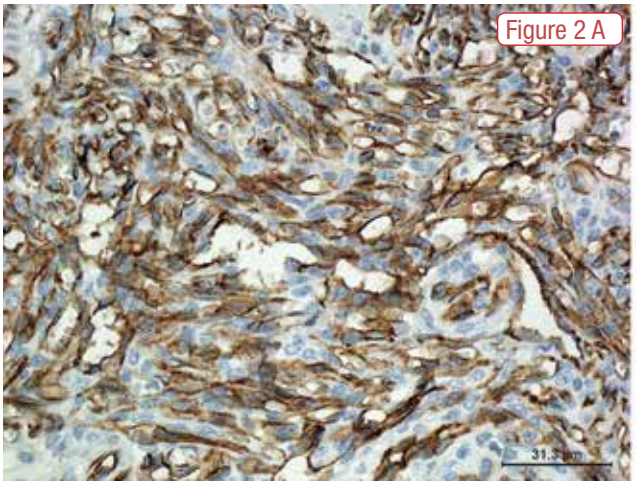

Figure 2A. CD31 immunopositivity confirming the endothelial origin of capillary and spindle-cell component of the tumour (x400).
Figure 2B. Podoplanin (D2-40) immunopositivity of cells in the periphery of tumour nodules confirming their partly lymphatic endothelial nature (x 100).

mechanical ventilation, administration of blood products and anticoagulants and antimicrobial therapy, an open surgical biopsy was performed.

Histopathology findings

One piece of tissue measuring 0.9 x 0.8 x 0.7 cm was analysed. Histologically, the tumour growth was in the form of partly coalescing nodules infiltrating the fat and fibrous tissue and surrounded by blood-filled vessels (Figure 1B). Some tumour nodules bulged into the outer crescent-shaped thin-walled vascular spaces, which is a pattern corresponding to the tufted angioma (TA) structures. These tumour components were associated with malformed, thin-walled, lymphatic vessels corresponding to the microcystic lymphatic malformation (Figure 1C). The tumour nodules were densely cellular with plump, spindled cells, arranged in haphazardly interlaced, sometimes tightly coiled, short fascicles interspersed with tiny capillaries and lining slit-like vascular channels filled with erythrocytes (Figure 1D). Immunohistochemical stains showed a diffuse CD31, CD34, and FLI-1 immunopositivity of tumour cells in the well-canalised and spindled areas (Figure 2A). These cells were GLUT-1 and HHV-8 immunonegative, but they expressed podoplanin (D2-40), mainly at the periphery of the nodules (Figure 2B). Tumour cells did not show significant atypia, the mitotic index was low, and around 5 % of tumour cells showed proliferative activity marked by Ki-67 immunopositivity. The histology of the tumour was entirely consistent with KHE with the TA component.

Therapy and course of the disease

Severe postoperative bleeding was stopped with intravenous administration of the activated recombinant factor VII (NovoSeven®) over three days. After establishing the diagnosis of KHE, intravenous corticosteroid therapy was instituted (initial pulse dose of 100 mg methylprednisolone, followed by 5 mg/kg/day). During the first two weeks of treatment, a significant reduction of tumour size was verified, along with reduced airway compression, re-expansion of the left lung, and improvement in respiratory function. The coagulopathy also subsided; platelet count rose to 309 x 10^9/L, and D-dimer levels decreased to normal. The dose of the corticosteroid was then reduced to 2.5 mg/kg/day. Two weeks later, clinical and radiological signs of tumour progression with the reappearance of the coagulopathy were observed. Subsequently, chemotherapy with vincristine (single dose of 1.5 mg/m^2) and three consecutive daily doses of cyclophosphamide (15 mg/kg) was initiated. Unfortunately, there was no response to this treatment and the infant's respiratory function deteriorated, leading to the reinstitution of mechanical ventilation. A fatal outcome occurred due to sepsis and respiratory failure within two months after the diagnosis was established. Parental consent for autopsy was not obtained.

Discussion

KHE is a rare, locally invasive, vascular tumour, initially described by Zukerberg et al in 1993 as

an infant skin lesions with ill-defined borders.[6] It is considered as a tumour of intermediate malignancy due to the absence of firm evidence of its metastatic potential.[7-9] Unlike considerably more common infantile haemangioma, KHE shows no tendency toward spontaneous regression nor immunohistochemical expression of GLUT-1.[5, 7]

Precise histopathological diagnosis of vascular anomalies and their categorisation according to the current ISSVA classification play a crucial role in the clinical management of patients since different types of malformations and tumours show great variability in response to advanced therapeutic modalities.[10, 11] Several reports suggested the existence of close clinical, histological and developmental relationship between KHE and TA,[7, 12, 13] which was also seen in current patient's tumour. Presently, these two entities are regarded as a continuum of the same vascular tumour (KHE/TA),[5, 14] sharing also the propensity for KMP and identical immunophenotype with an expression of podoplanin and PROX-1.[5, 7]

Vascular tumours with a predominantly spindle-cell component represent a diagnostic challenge for a histopathologist because of the morphologic overlap between different entities with varying malignant potential.[15] In addition to the striking differences in clinical presentation, each of these tumours is different from KHE in the following histologic details: (1) spindle cell haemangioma has a biphasic composition with cavernous vascular spaces and more solid spindle-cell areas containing cytoplasmic vacuoles; (2) in nodular phase of Kaposi sarcoma there is no lobular arrangement of the spindle cells, which are also invariably HHV-8 immunopositive; (3) spindle cell variant of angiosarcoma is characterised by an infiltrative growth and multilayering of more atypical endothelial cells at the periphery of the lesion.[7, 8, 15] A recently defined entity, kaposiform lymphangiomatosis (KLA), shares overlapping patterns of clinical symptoms (including KMP), anatomical location, imaging features and complications with KHE. KLA has features of both tumours and malformations of the lymphatic vessels, grows diffusely or multifocally, often in the mediastinum and lungs, and its histological hallmark is the presence of poorly marginated clusters and sheets of kaposiform spindled cells oriented in parallel fashion amidst abnormal, dilated lymphatic channels. With diffuse lymphatic markers immunoreactivity, such histological picture is still different from KHE.[16]

Just over two-thirds of patients with KHE/TA develop KMP, which is defined as an accumulation of platelets and coagulation factors within lesions followed by thrombocytopaenia and consumption coagulopathy with a consequent life-threatening haemorrhage and a mortality rate estimated at 10 - 30 % of infants.[6, 9, 13, 14, 17-20] KMP is more common in patients with KHE located in deep tissues extending into multiple anatomic regions (78 % of patients) than in patient with superficial lesions (36 %).[20] The identified risk factors for KMP also include larger tumour size, multifocality and depth of tumour infiltration, as well as an intrathoracic, intra- and retroperitoneal location.[12, 14, 17-21] There is also a higher incidence of KMP in females and younger patients,[9, 14, 18, 20] (79 % of infants; 10% of adolescents).[14] KMP is associated with more aggressive KHE and worse disease outcomes,[21] which may be also related to more frequent compression of vital structures.[18]

The strategies used so far in the treatment of KHE can be divided into three groups: (1) resection/interventional procedures, including vascular embolisation or ligation, (2) irradiation, (3) antiangiogenic drugs, chemotherapy agents and anticoagulation substances. The best option for KHE treatment is a complete surgical resection, if it is achiavable.[9, 12, 14] According to the literature, the most frequently used medical treatments were, in descending order: steroids, vincristine, interferon alpha, platelet aggregation inhibitors, sirolimus and propranolol.[9, 14] In the case of the patient presented in this paper, the enormous size of the tumour and its relation to vital mediastinal structures, association with severe coagulation disorder and only partial responsiveness to conservative treatment made radical surgery impossible at the time. In the absence of definitive guidelines for the pharmacological treatment of KHE, the most common combination of applied medical therapy was steroids/vincristine,[9, 14] which was also tried in this particular patient, but with the addition of cyclophosphamide. A good therapeutic response could be achieved in 30 - 43% of patients.[14] At the time of this patient' treatment, there were no reports on the usefulness of the inhibitor of mammalian target of rapamycin (mTOR) sirolimus in the treatment of vascular lesions. Since many studies have demonstrated a very effective response to sirolimus treatment, it is now considered the first-line therapy for KHE and KMP.[14, 19, 22]

So far, two of the most comprehensive KHE studies have included 107 patients from a US centre

(published in 2013)[20] and 146 patients from a Japanese centre (published in 2018).[18] Schmid et al. registered that 105 publications concerning KHE were written in English and German language between 1993 and 2017.[14] The prevalence of KHE has been estimated at 0.91 per 100.000 children.[20] The majority of KHE cases occurred in infancy (about two-thirds of all) and the numbers decreased with increasing age, being slightly more frequent in males.[9, 14, 18, 20]

KHE is most commonly located in the dermal and subcutaneous tissue of extremities, trunk and neck, face and head region.[9, 14, 18, 20] According to the most significant series of data, KHE extends to more than one region in 7 - 26 % of cases. KHE is noted in the extracutaneous site in 11 - 17 % of patients[14, 18, 20] and 3 - 10 % are found in the intrathoracic location.[18,20]

Regarding the incidence of mediastinal lesions in childhood, mesenchymal tumours rank second (18.2 % of 137 lesions), after neurogenic (34.3 %), and followed by lymphoid neoplasms (16.8 %).[23] Only 2.2 % of mediastinal lesions are diagnosed as haemangiomas,[23] although in some analyses even lower incidence was reported.[24]

After a systematic literature search in the Medline database (http://www.ncbi.nlm.nih.gov/pubmed/), it was found that only 18 cases describing patients with mediastinal KHE location had been published so far. In 2014, Wallenstein et al[25] summarized 12 previously reported cases of mediastinal KHE and added one case of their own. Following this review, to date, only five new cases of mediastinal KHE were published in the English.[19, 17, 26] In one of these cases, the exact age of patient remained unknown,[19] while in two cases gender of patients was missing.[13,19] After the inclusion of the present case in the calculation, the age of patients at the time of tumour detection ranged from soon after birth to 60 months, with 15 out of 18 (83 %) patients being in the infant age. A male/female ratio was 7 : 9. KMP developed in all but one patient.[9] Majority of patients had compression of vital structures (trachea, bronchi, large blood vessels) with respiratory failure and some of them had pericardial and/or pleural effusions at presentation. In four patients, the tumour spreading to the neck tissue was registered[13, 17, 26, 27] and in one patient KHE was multifocal.[17] In all patients, the tumour was inoperable at the time of diagnosis. Under the influence of different modalities of medical therapy, the course of the disease was characteristically variable. Four of 19 patients died (21 %). Two died due to KMP-related haemorrhage[27] and respiratory distress,[17] the others due to sepsis which had developed after partial tumour resection.[13] The patient presented in this paper also deceased after tumour biopsy followed by medical therapy. In other patients, regression of tumour mass and KMP was eventually noted, but residual tumour tissue persisted after variable follow-up periods.[17, 19, 25, 26]

The reported mortality rate related to KHE ranges from 10 - 25 %.[9] In the recent retrospective study of Schmid et al 9 % of 191 followed patients died from complications of the disease (bleeding, disseminated intravascular coagulation, aspiration pneumonia, compression of airways, sepsis).[14] Based on the literature data, adverse prognostic factors in patients with KHE significantly overlap with the risk factors for the development of KMP that were previously mentioned in this article.[9, 14, 16, 18-21, 28] However, the result of the present analysis of 19 cases shows that the mortality rate from mediastinal KHE is close to the upper limit of the mortality rate from KHE of all anatomical sites, but does not exceed it. This is consistent with the latest analysis of Ji et al,[18] in which tumour location failed to reach independent prognostic significance in the multivariate statistical analysis.

Conclusion

It can still be concluded that, in the case the patient presented in this article, several risk factors for adverse outcomes were present: onset of disease in early infancy, large dimensions of the tumour, mediastinal location, KMP and partial response to the available therapy. Although exceptionally rare, KHE must be included in differential diagnostic considerations when dealing with a fast-growing mediastinal mass associated with respiratory problems, coagulopathy and profound thrombocytopaenia, especially in a patient in the first year of life.

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None.

Conflict of interest

None.

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