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Case Report

Bone Marrow Langerhans Cell Histiocytosis in Association with Kasabach-Merritt Syndrome: The Difficulty of a Differential Diagnosis

Joao Tiago Serra Raquel Silva Fernando Aldomiro Fernanda Paixao Duarte

Department of Internal Medicine II, Professor Doutor Fernando Fonseca Hospital, Amadora, Portugal

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Langerhans cell histiocytosis · Kasabach-Merritt syndrome · Idiopathic thrombocytopenic purpura · Intravascular disseminated coagulopathy · Tuberculosis

Abstract
Langerhans cell histiocytosis is a rare haematological disorder with variable clinical findings and a high mortality rate. On the other hand, Kasabach-Merritt syndrome is of rare onset at adult age, requiring the simultaneous presentation of vascular lesion, thrombocytopenia, and consumptive coagulopathy. We present the first reported case of both diseases in a single patient and highlight the difficulties of diagnostic. A 69-year-old woman with immune thrombocytopenic purpura underwent surgery for the removal of giant skin haemangiomas. During post-operative care, intravascular disseminated coagulopathy developed. After weeks of corticosteroids and immunosuppressive therapy with no clinical improvement, pulmonary tuberculosis was diagnosed and appropriate treatment initiated. Despite all the efforts, the patient's clinical condition kept worsening and she eventually died. An autopsy revealed bone marrow Langerhans cell histiocytosis. In this case, the patient's autoimmune background together with tuberculosis and intravascular disseminated coagulopathy masked the presentation and made the diagnosis of a rapidly progressive fatal disease very difficult.

Introduction

Langerhans cell histiocytosis (LCH) is a rare disease of unknown aetiology, characterized by a proliferation of lymphocytic cells with specific morphology, ultrastructure, and phenotype [1]. Although usually diagnosed in young children, it can occur in adulthood with an estimated incidence of 1–2 cases per million, mostly caucasian males [1, 2]. The pathogenesis remains

Joao Tiago Serra
Department of Internal Medicine II
Professor Doutor Fernando Fonseca Hospital
IC-19, PT–2720-276 Amadora (Portugal)
joao.t.serra@gmail.com

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unclear, contributing to the indecision on whether LCH should be considered a hyperplastic reactive disorder or a neoplasm. Diagnosis can be misleading, since clinical features vary from an asymptomatic solitary lesion to a lethal multisystemic disease. In the latter case, any organ can be involved, but bone and skin are more commonly affected [3]. The current standard of care for LCH is based on site and disease extension, with a survival rate of less than 50% for high-risk patients [2, 4].

Kasabach-Merritt syndrome (KMS) rarely presents in adults, occurring almost exclusively in infants and young children. The diagnosis requires a triad of a vascular lesion, thrombocytopenia, and consumptive coagulopathy [5, 6]. KMS pathogenesis is poorly understood, although platelet and fibrinogen consumption by intralesional thrombosis are accepted as the underlying mechanism [7]. There are currently no guidelines for the management of KMS, but the general approach is to control coagulopathy with supportive care and medical therapy [5].

We present the first known case of an association between these two rare conditions, briefly review the underlying literature, and focus on the clinical manifestations and the difficulties of differential diagnosis.

Case Report

A 69-year-old caucasian woman was admitted to our hospital for the removal of giant dorsal haemangiomas. Multiple scattered cutaneous vascular lesions had emerged in recent years (Fig. 1) and prompted excision surgery before. There was also a medical background of immune thrombocytopenic purpura for more than 30 years, under long-term treatment with corticosteroids and immunosuppressants (cyclosporine and azathioprine), and multinodular goitre associated with hyperthyroidism. There was no history of smoking and besides the haemangiomas, there were no other lung, skin or constitutional symptoms.

At admission, the platelet count was 75,000/μL (reference range [RR] 150–400); however, after the procedure, it dropped to 19,000/μL, and there was active bleeding from the surgical incisions. Methylprednisolone pulses were administered, and immunosuppressive therapy was maintained with the platelet count increasing to 47,000/μL and successful bleeding control. Nevertheless, during the following weeks, the patient's condition kept worsening with ascites and bilateral relapsing pleural effusion development. Paracentesis, thoracentesis, and bronchofibroscopies were performed, but although with characteristic exudative fluids, no pathological agents or malignant cells were ever identified.

At this point, blood analysis showed Hb 7.6 g/dL (RR 11.5–16.5), white blood count 14.9 × 10^9/L (RR 4–11), platelet count 3,000/μL, D-dimers 35,923 μg/L (RR <500), fibrinogen 1.2 g/dL (RR 1.5–4.0), C-reactive protein 5.97 mg/dL (RR <0.30), FT4 3.02 ng/mL (RR 0.8–1.76) and TSH 0.006 mIU/L (0.55–4.78). Blood and urine cultures were positive for *Enterococcus faecium*. A diagnosis of disseminated intravascular coagulopathy (DIC) in a patient with KMS and sepsis was made. Immunoglobulin, methylprednisolone, plasma, and cryoprecipitate, together with broad-spectrum antibiotics were administered. Platelets stabilized at around 30,000/μL, but a consumptive state with marked weight loss and clinical worsening kept progressing. A full-body CT scan was performed with no evidence of tumours, lymphadenopathies, or bone lesions.

After weeks, a Löwenstein-Jensen culture from bronchoalveolar lavage became positive for *Mycobacterium tuberculosis*. Standard antibacillary treatment was initiated; however, due to hepatotoxicity, the therapeutic scheme had to be readjusted. More than 4 months after admission, the patient was discharged on maintenance antibacillaries, corticosteroids, immunosuppressive therapy, and antithyroid drugs.

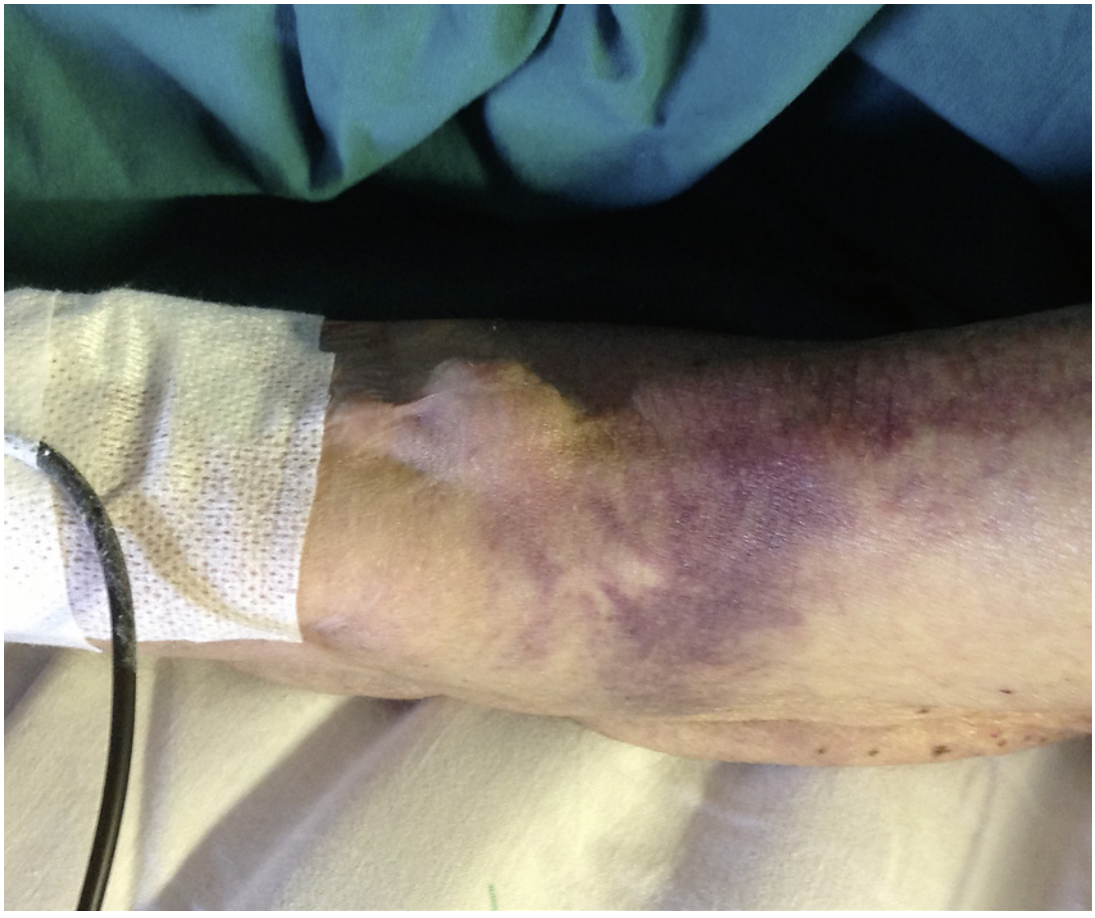

Fig. 1. Haemangioma on the anterior side of the left arm near the elbow joint.

Within 2 months she was readmitted due to an extensive left pleural effusion causing dyspnoea and respiratory insufficiency. Blood analysis showed Hb 10.1 g/dL, platelet count of 3,000/μL, alkaline phosphatase 196 IU/L (RR 50–136), GGT 308 IU/L (RR 5–55) and C-reactive protein 11.10 mg/dL. Although no bone lesions had been identified so far, a bone marrow aspirate was performed and showed only a reactive bone marrow without signs of pathogens or malignant cells.

Active gastrointestinal bleeding eventually arose with the haemoglobin level dropping to 4 g/dL. Rescue therapy with rituximab was attempted with a platelet count increase to 42,000/μL and a D-dimer drop to 2,400 μg/L. Despite all the diagnostic and therapeutic efforts the patient died.

A post-mortem examination revealed bone marrow infiltration by large cells with an irregular core and large cytoplasm (Fig. 2a, b). Immunohistochemistry was positive for CD1a, S100, and CD5, and negative for markers of plasmacytic, B- and T-cell differentiation (Fig. 2c). Electron microscopy identified Birbeck granules (Fig. 2d). The cause of death was established as LCH.

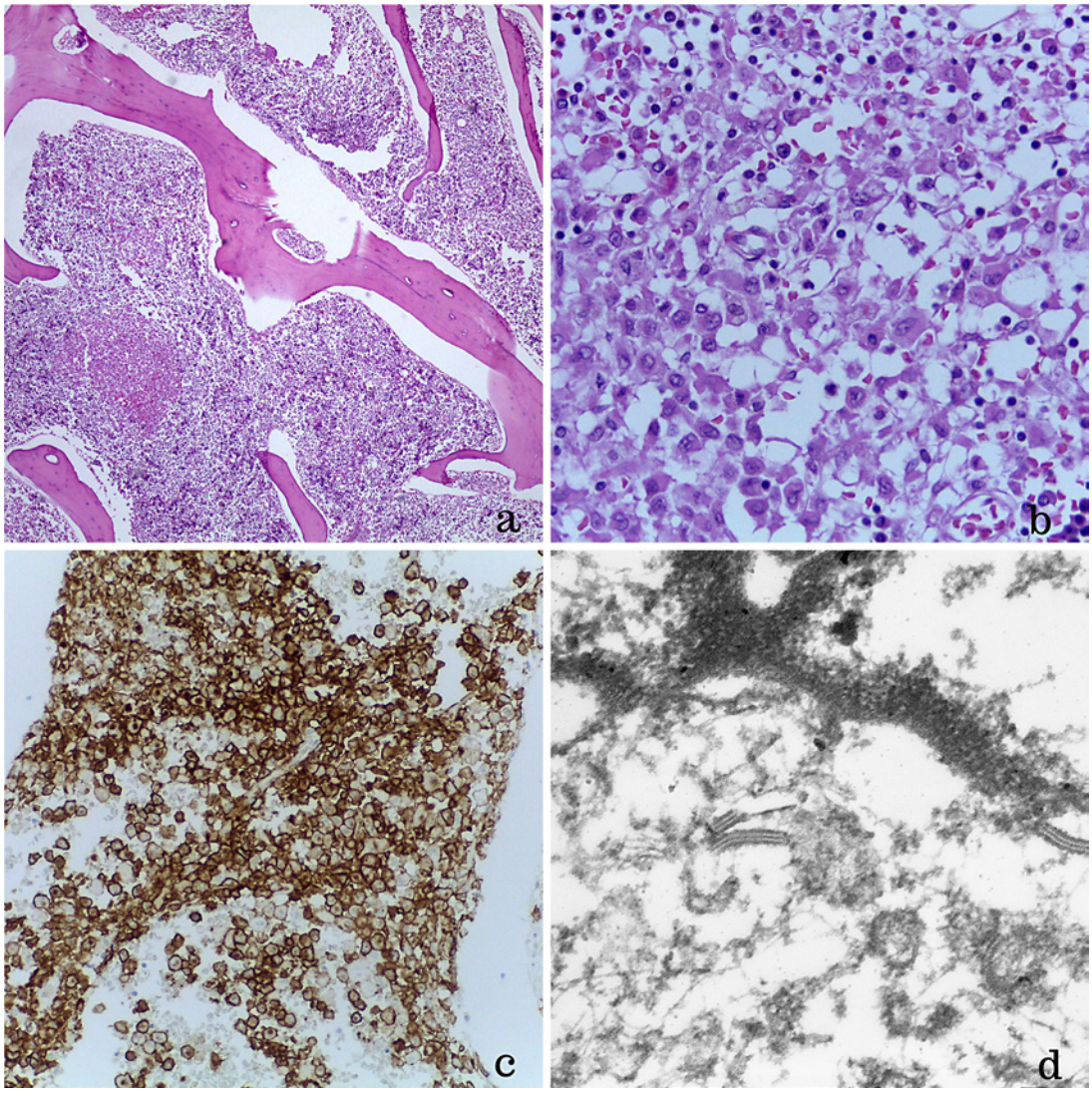

Fig. 2. Post-mortem histological images of the bone marrow. **a** Hypercellular intertrabecular space. H&E. ×4. **b** Cell population with large eosinophilic cytoplasm and cerebriform nucleus. H&E. ×20. **c** Positive immunohistochemical staining for CD1a marker. CD1a+. ×20. **d** Electron microscopy showing "tennis-racket" cytoplasmic organelles characteristic of Birbeck granules. ×40,000.

Discussion

As far as we know this is the first time KMS and LCH have been simultaneously described. In adulthood, KMS usually occurs as a complication of haemangiomas, haemangiomatosis, or angiosarcoma, and there are a few literature reports of angioma development after treatment with immunosuppressive agents [8, 9]. This might have been the case in our patient, since multiple vascular skin lesions arose after years of cyclosporine and azathioprine treatment. From another perspective, DIC is a serious and potentially fatal acute complication of KMS, which has previously been reported after surgically related procedures [10].

In the autopsy report, LCH turned out to be the established cause of death, although diagnosis was only achieved post-mortem. The clinical manifestations of LCH can vary widely depending on the age of onset, proliferative rate of Langerhans cells, and the organ or system

affected [1]. Skin disease may be the primary presentation, but it can be easily misdiagnosed due to the many different presentations mimicking common dermatological conditions, and so requiring a high level of suspicion for early detection [4]. In this case, giant skin haemangiomas related to KMS were the dominant problem, masking other skin lesions that might have been present.

Immunosuppression-related conditions such as *M. tuberculosis* infection, not only led to the misinterpretation of eventual clinical and radiological LCH lung affection, but were also the main explanation for the marked weight loss and consumptive state which were thought to be tuberculosis related.

The clinical suspicion of a malignant disease was always present, even though all examinations carried out including a full-body CT scan had not identified any tumours, bone lesions, or lymphadenopathies. Thyroid ultrasound and function abnormalities were related to the long-term multinodular goitre and did not show any signs of malignancy.

With the development of DIC and acute gastrointestinal bleeding, rescue therapy with rituximab was attempted without success [11]. Despite all the efforts, the patient's clinical condition kept worsening and she eventually died. The post-mortem examination revealed a bone marrow and lymphatic system LCH. As stated before, this is an extremely rare condition in the adult population, particularly with such an aggressive course [4, 12].

The differential diagnosis of LCH includes reactive histiocyte hyperplasia in systemic infections, storage diseases, or haemophagocytic lymphohistiocytosis [13]. DIC, KMS, and tuberculosis played a major dissimulating role in this case, since not only skin, lung, and consumptive findings were attributed to these conditions, but also prevented other diagnostic invasive examinations such as a bone marrow biopsy due to severe anaemia and thrombocytopenia.

Findings suggest that LCH cells are more likely to arise from dysregulated differentiation or recruitment of bone marrow-derived precursor cells rather than from transformed or activated epidermal Langerhans cells [2,3]. In our case, the continuous state of inflammation related to severe infection, combined with a medical background of autoimmunity, might have been the cornerstone for LCH development.

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Statement of Ethics

Written informed consent for publication (including images) has been obtained from the patient's relatives.

Disclosure Statement

The authors declare that they have no conflict of interest.

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Author Contributions

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