Erdheim-Chester Disease in a 48-Year Old Woman with “An Unknown Tumour of the Heart:” An Autopsy Report.

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Case Report

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Abstract

Erdheim-Chester disease (ECD) is a rare non-Langerhans cell histiocytosis. ECD is considered a potentially severe multi-systemic disease with life-threatening manifestations due to the compression of normal structures. Recently, mutation of the proto-oncogene BRAF (BRAFV600E) has been found in 100% of cases. The common sites of involvement are the skeleton, central nervous system, cardiovascular system, lungs, retroperitoneum and skin.

We present the autopsy case of a 48-year old caucasian woman with an unknown tumour of the heart, where autopsy revealed the diagnosis of ECD. The clinical, radiological, and pathological manifestations associated with ECD are highlighted.

1. Introduction

Erdheim-Chester disease (ECD) is a rare non-Langerhans histiocytosis characterized by severe fibrosis accompanied by an infiltration of CD68-positive, CD1a-negative macrophages and multinucleated giant cells as well as proliferation of lymphocytes. It is considered a neoplasm of myeloid origin(1). ECD is associated with mutations of kinase signalling pathways e.g. BRAF, NRAS and KRAS(2). ECD can involve all organ systems e.g. lungs and heart, and is considered a potentially severe multi-systemic disease with life-threatening manifestations due to the compression of normal structures (3). Currently there are no evidence-based clinical guidelines that address treatment of ECD. Treatment can involve targeted therapy (in consideration of the underlying mutation) e.g. BRAF inhibition and MEK (MAPK/ERK Kinase) inhibition (2). Other treatments involve Interferon-alfa and glucocorticoids(4).

We report the autopsy findings in a 48-year old caucasian woman with a massive tumour growth involving heart and pericardium, lungs, central veins and retroperitoneum. Histopathology revealed a fibrous proliferation with a mixture of lymphocytes, plasma cells and abundant histiocytes, including multinucleated giant cells, and BRAF V600E mutation, compatible with ECD.

2. Case Presentation

2.1 Background

A 48-year old woman succumbed to heart failure due to an inoperable heart tumour, which was diagnosed four years earlier.

Initially she was admitted due to oedema and a weight gain of 5 kg over the previous 10 days, combined with fever, headache and abdominal pain. She had no significant medical history prior to this. A CT scan revealed pericardial effusion, widespread inflammation in the retroperitoneum, and sclerotic lesions in the spine and pelvis. Diagnostic workup (including cytologic investigation) did not suggest malignancy or infection. During the subsequent six months, she was admitted several times due to recurrent idiopathic pericardial effusion.

Eventually, a MR-scan of the heart disclosed a mass involving the right ventricle, the right atrium, and partially the left atrium, highly suspicious of neoplasia.

The patient was operated to obtain a biopsy for histologic diagnosis, and to resect the tumour if possible.

At surgery, the pericardium had multiple soft adherences and appeared inflamed and in some areas covered by fibrin. Pericardial fluid was abundant. Dense tumour-tissue was found incorporated as a band located at the lateral side of the right atrium stretching from the superior to the inferior caval vein, approximately 2 cm thick, and protruding somewhat into the atrial cavity. Tumour tissue was also found to be incorporated in the anterior wall of the right ventricle as an approximately 4 cm wide band arching along the atrio-ventricular groove, encroaching the right coronary artery, and following the acute margin to the apex of the heart. The rest of the anterior wall of the right ventricle had no evidence of tumour invasion. The tumour was pale and sparsely vascularised. Biopsies were obtained for histology. The tumour was technically impossible to resect.

Histology revealed a mass of mainly fibrous tissue, mixed with chronic inflammatory cells, oedema and abundant minor vessels. Solitary fibrous tumour was considered a plausible diagnosis, as well as some kind of reactive fibrous condition. But no unambiguous diagnosis was concluded.
The possibility of heart transplantation was discussed, but initially rejected because the patient suffered few symptoms at this stage. When she finally was considered sick enough (!), a transplant was deemed impossible as the tumour seemed to involve the large vessels.

One year after the first biopsy, and approximately 2.5 years before death, a trans-venous myocardial biopsy was performed. Histopathology showed the same changes as earlier. Neoplasm, including malignancy, was considered. A solitary fibrous tumour was re-considered, but the diagnosis was decided to be: "Unspecific chronic inflammation and fibrosis." The sections were seen by several pathologists.

She was treated symptomatically as a heart failure patient and over the next couple of years her symptoms, (dyspnoea, fatigue, oedema) worsened dramatically, and she was no longer able to work nor perform daily life activities. She was admitted several times, acutely as well as electively. Finally she was transferred to a hospice where she eventually died (4 years after initial consultation).

2.2 Autopsy findings

External examination revealed no abnormal pathology beside a 30 cm long sternotomy scar. Internal examination of the thoracic cavity revealed a massive fibrous pale tumour growth, measuring 27 cm, surrounding the heart, involving the pericardium as well as the cavities of both atria and ventricles (Fig. 1a-b). Locally the mass was seen infiltrating the myocardium. All three lobes of the right lung were infiltrated by the mass. The left lung was compact and displaced cranially, but seemed uninvolved by the tumour mass. The mass was adherent to the thoracic wall and the thoracic spine.

An identical pale mass, measuring up to 4.5 cm in diameter, was surrounding the thoracic and abdominal aorta, as well as the renal arteries and the inferior caval vein. The mass also involved the retroperitoneum, infiltrating the renal fat patch and the small intestinal mesentery, as well as the peripancreatic and periadrenal tissue bilaterally, and a small area of the liver capsule. There seemed to be no involvement of the organs.

The histopathologic changes were identical in all samples (Fig. 1c, 2–3), showing a fibrous proliferation with a mixture of small lymphocytes without atypia, plasma cells, and abundant histiocytes, including a few histiocytic giant cells. The histiocytes stained positively for CD68 and negatively for CD1a. Only a few IgG4 positive plasma cells were seen. No microorganisms were shown. The lung tissue showed a distinct distribution with involvement of pleura, interlobular septa and bronchovascular bundles while the intervening alveolar parenchyma was spared. The bone marrow revealed no myeloid dysplasia or accumulation of histiocytes

BRAF$^{V600E}$ mutation was found in histiocytes in sections from the pericardium, lungs and retroperitoneum.

Based on the characteristic anatomic distribution of disease combined with histopathology and BRAF$^{V600E}$ mutation, ECD was finally diagnosed.

3. Discussion

ECD is a rare neoplasm of myeloid progenitor cells with characteristic radiologic and histologic features involving severe fibrosis accompanied by an infiltration of CD68 positive and CD1a-negative macrophages and multinucleated giant cells, as well as a proliferation of lymphocytes. Recent studies have demonstrated BRAF$^{V600E}$ mutation in up to 100% of cases, and it appears that BRAF and/or other signalling molecules drives the proliferation process (5) There is no firm evidence that ECD is inherited; the mutations associated with ECD seems to be acquired (4).

Since the disease first was described in 1930 by Jakob Erdheim and William Chester nearly 1000 cases has been reported (3), and around 400 of these in the last five years (6). ECD can involve all organ systems, and is considered a severe multi-systemic disease with life-threatening manifestations, but has also been described asymptomatic in some patients (7). Most frequently (> 95% of cases) is involvement of the skeleton, where the long bones are primarily affected, emerging as symmetrical osteosclerosis (8). Involvement of the axial skeleton has also been described (9). Involvement of the skeleton is often asymptomatic. At her first admission CT-scans had revealed osteosclerosis of the spine and sacroilliac joints. Unfortunately the status of the long bones could not be accessed from existing scans. In other words ECD was not suspected.
Lung involvement is found in up to 59% of described cases, generally leading to chronic dyspnoea (10). Characteristic histopathologic changes include fibrosis accompanied by histiocytic and lymphoplasmacytic infiltrates with involvement of pleura and interlobular septa, and a distinct peri-bronchovascular distribution (11). The characteristic histopathologic changes of the right lung revealed the diagnosis in this case.

The most frequent cardiovascular findings, present in 66% of all cases (12) are periaortic fibrosis ("coated aorta"), and involvement of aortic branches and pericardium (13). In addition to this, abnormalities as pseudo-tumoral infiltration of the right atrium, pericardial effusion and thickening, and infiltration of the coronary arteries, are also frequently seen (13). Our patient initially presented with recurrent pericardial effusion and retroperitoneal engagement.

Our patient was diagnosed 4 years prior to her death with "an unknown tumour of the heart," even though a final histopathologic diagnosis of neoplasm was never given. She was affected by chronic dyspnoea, which was believed to be caused by heart failure and was never seen by a pulmonologist, which could have led to a lung biopsy and perhaps a diagnosis. Biopsies from the heart were performed twice, respectively four and three years before death, showing a mass of mainly fibrous connective tissue, mixed with chronic inflammation and abundant vessels. Malignancy was ruled out each time.

Had a diagnosis of ECD with BRAF V600E mutation been obtained while the patient was alive, treatment with BRAF inhibitors might have been tried, as promising results have appeared (2, 14). A study by Cohen et all. involving 22 ECD patients with BRAF V600E mutation, 5% achieved overall response and 5% complete response(14). Earlier Interferon-alfa and glucocorticoids have been used with some success (15). The five-year survival rate of ECD patients treated with Interferon-alfa was 68% in a study by Arnaud et all. (15)

In retrospect, the result of CT and MR-scan with bone changes and retroperitoneal fibrosis, echocardiography and biopsy in combination with clinically symptoms should have led to the in vivo diagnosis of this rare disease, and relevant treatment might have been implemented.

4. List Of Abbreviations

ECD: Erdheim-Chester disease

MEK: MAPK/ERK Kinase

5. Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

'not applicable' (the text does not include information/pictures etc that make the traceable.

Availability of data and materials

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Authors’ contributions

Autopsy was performed by Louise A. Lynggård. Louise A. Lynggård and Ulrik Baandrup wrote the initial draft of the manuscript. All other authors have critically reviewed the manuscript and approved the final, submitted version.

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