Histiocytosis X and Pericarditis - A Rare Association and a Difficult Diagnosis

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ABSTRACT: Histiocytic disorders are a group of rare diseases with systemic involvement and with multiple clinical manifestations. We present the case of a 51 years old patient investigated for dyspnea with orthopnea, dry cough, asthenia, muscular weakness and ataxia. The association of previous symptoms with skin lesions, diabetes insipidus, partial hypophyseal insufficiency and pericarditis induced many diagnostic debates. The diagnosis is Histiocytosis X must be sustained by tissue biopsy with immunohistochemical assay or genetic testing. The particularity of our patient is the presence of pericarditis, rarely associated with histiocytosis. Collaboration between medical specialties is mandatory in order to treat this disorder.

KEYWORDS: pericarditis, histiocytosis X, xantelasma, diabetes insipidus, pituitary failure

Introduction

Histiocytic disorders are a group of rare diseases (1-2 adults per million people) that occur when there is an accumulation of monocytes, macrophages, and dendritic cells that can lead to organ damage and tumor formation.

Over the last 5 decades, because of the many clinical manifestations and of the variable severity depending on organ involvement, these disorders carried different names. [1]. For instance, Hand-Schüller-Christian disease, the eosinophilic granuloma and Abt-Letterer-Siwe disease were considered different entities, but now, it has been proved that they are the manifestations of a single entity: Langerhans cell histiocytosis (LCH).

The overall male-to-female ratio is 1.5:1. In case of involvement of only one organ, the male-to-female ratio is 1.3:1, while in case of multisystem disease the male-to-female ratio is 1.9:1. [2]. LCH can occur in individuals of any age. [3, 4, 5, 6, 7, 8, 9, 20]

The classification of histiocytic disorders the World Health Organization (WHO) [11] has proposed it as follows:

- Class I - Langerhans cell histiocytosis - most common
  - Class II
    - Histiocytosis of mononuclear phagocytes other than Langerhans cells
    - Familial and reactive hemophagocytic lymphohistiocytosis (HLH)
  - Sinus histiocytosis with massive lymphadenopathy (SHML), Rosai-Dorfman disease
    - Juvenile xanthogranuloma (JXG)
    - Reticulohistiocytoma
      - Class III
    - Malignant histiocytic disorders
    - Acute monocytic leukemia (FAB M5)
    - Malignant histiocytosis
    - True histiocytic lymphoma

Clinical presentation varies significantly. Lungs are affected in 20% up to 40% of patients with nodular infiltrate, pleural effusion, cystic changes, all evolving towards pulmonary fibrosis. Main symptoms are: dyspnea, cough, tachypnea [12]. Brain can be infiltrated, including cerebellum, with ataxia and loss of coordination, disorders of the hypothalamic and pituitary functions manifested as diabetes insipidus and total or partial hypopituitarism [13, 14, 15]. Cutaneous manifestations are found in up to 50% of patients with LCH and they may present as maculouerythematous skin infiltrates, nodular popular, petechial xantomatous. Bones can be affected: singular or multiple osteolytic lesions of vertebrae, orbits, skull, long bones, sometimes with important periosteal reaction. Lymph nodes enlargement and gastrointestinal bleeding or liver dysfunction can also occur but in lesser extent.

The etiology of these disorders is not entirely known. It seems that many factors are involved: genetic, triggered by an infection (most frequently viral), cellular or immune
dysfunction, neoplastic mechanisms etc. [16, 17, 18, 19].

The diagnosis is based on clinical assumptions but it must be confirmed either through skin biopsy, bone marrow biopsy, lung biopsy [revealing LCH cells positively stained with antibodies to CD1a, S100 and/or anti-langerin (CD207)] or by genetic proof of BRAF mutations [20].

Even if sometimes, quite rare, the disease can be self-limited, in the majority of cases, especially with multiple organs involvement, it cause significant mortality. The main treatment in LCH is chemotherapy (usually Vinblastine) and corticoid treatment [21].

The prognosis depends on the severity of symptoms and on the multitude of involved organs. Usually, a good prognosis is associated with a good response to treatment in the first six weeks.

**Case presentation and discussions**

We present the case of patient of 51 years old, female, who was admitted in the II Medical Clinic of the Clinical Emergency Hospital of Constanta in October 2016 for dyspnea at rest with orthopnea, dry cough, important asthenia, muscular weakness and ataxia.

From her medical history we retain that 11 months before the actual admission the patient suffered two episodes of pericarditis and pleurisy which required pericardiocentesis and, in the same time, she was diagnosed, also 11 months ago, with pulmonary fibrosis, pituitary adenoma stage I/II Hardy, hyperprolactinemia, central diabetes insipidus and partial hypophyseal insufficiency. Treatment with desmopresine and cabergoline was initiated at the time.

Physical examination revealed an overweight patient with xantelasma and xantoma, with multiple macular areas and pigmented nevi with dimensions between 2 and 9 mm, spread on the entire body. The patient had important ataxia and mild cognitive disorder. Respiratory system’s examination revealed bilateral subcrepitant rales and abolished breath sound in the left pulmonary base. Heart sounds were weak and tachycardic and mild jugular veins distension observed. No galactorrhea was found, either the moment of examination, or in her history, as well as no visual field disorders but a goiter of I degree with multinodular appearance. Patient’s fluid ingestion was controlled under treatment with 0.1 mg of desmopresine.

![Fig.1. Xantelasma](image)
Fig. 2. Generalised skin eruption (dermatofibromas)

Chest X-Ray and thoracic computed tomography (CT) confirmed the presence of pericarditis in medium amount, left pleural effusion, pulmonary fibrosis.

Fig. 3. Chest X-Ray revealing enlarged heart and pulmonary fibrosis

Fig. 4. Thoracic CT revealing pericarditis and left pleurisy

Laboratory investigations revealed elevated ESR, serum fibrinogen and C reactive protein, leukocytosis with neutrophilia, mixed dyslipidemia, negative HIV tests, low PRL, FSH, LH, IGF-1, 25-OH-D2 vitamin, normal values of serum cortisol, TSH, FT4, ACTH, PTH, angiotensin convertase, serum calcium.

Table 1. Umoral parameters of the patient

| Parameter                  | Value            | Reference Range          |
|----------------------------|------------------|--------------------------|
| Hb (g/dl)                  | 13.3             | 11.7-16                  |
| White blood count (elements/mm³) | 22550         | 4000-10000               |
| Platelets (elements/mm³)   | 717000           | 150000-450000            |
| Hematocrite (%)            | 41.5             | 35-47                    |
| ESR (mm/h)                 | 35               | <20                      |
| Fibrinogen (mg/dl)         | 574              | 200-400                  |
| CRP (mg/dl)                | 6.99             | <0.5                     |
| Glycemia (mg/dl)           | 99               | <100                     |
| ALAT (ui/dl)               | 4                | <33                      |
| ASAT (ui/dl)               | 20               | <35                      |
| Urea (mg/dl)               | 32               | <43                      |
| Creatinine (mg/dl)         | 0.63             | <1                       |
| Cholesterol (mg/dl)        | 206              | <200                     |
| Triglycerides (mg/dl)      | 227              | <150                     |
| Serum proteins (g/dl)      | 6.6              | 6.6-8.7                  |
| PRL (µUI/ml)              | 9                | 12-7-637 (under cabergoline treatment) |
| TSH (µUI/ml)               | 1.39             | 0.27-4.2                 |
| FT4 (pmol/l)               | 11.9             | 10.6-22.7                |
| Serum cortisol am (mmol/l) | 357              | 171-536 (7-10 am)        |
| FSH (mUI/ml)               | 3.1              | 25.8-134.8 (menopausal)  |
| LH (mUI/ml)                | 0.8              | 7.7-58.5 (menopausal)    |
| Serum Na (mmol/l)          | 141              | 136-145                  |
| Serum K (mmol/l)           | 4.9              | 3.5-3.1                  |
| PTH (pg/ml)                | 25.2             | 15-65                    |
| Phosphomenia (mg/dl)       | 4.1              | 2.5-4.5                  |
| ACTHpg/ml                  | 9.35             | 7.2-63.3                 |
| IGF-1 (ng/ml)              | 51.23            | 57-236                   |
| 25-OH vitamin D (ng/ml)    | 10.4             | 30-100                   |
| p ANCA (u/ml)              | <0.7             | <7                       |
| c ANCA (u/ml)              | <0.2             | <7                       |
| C3c (mg/dl)                | 132              | 90-180                   |
| C4 (mg/dl)                 | 28               | 10-40                    |
| ACE (u/l)                  | 15               | 12-68                    |
| Ca ionic (mg/dl)           | 4.3              | 3.8-4.82                 |
| Serum total Ca (mg/dl)     | 8.6              | 8.6-10                   |
| Antibodies anti HIV 1+2    | negativ         |                          |

ACE=angiotensin-converting enzyme
ACTH=adrenocorticotropic hormone
ALAT=alaninaminotransferaze
ASAT=aspartataminotransferaze
CRP=C reactive protein
cANCA=antibodies anti-proteinase 3
pANCA=antibodies anti myeloperoxidase
FSH=follicle stimulating hormone
PTH=parathormone

Thyroid ultrasound confirmed the micronodular aspect of the thyroid.

The cardiologic examination confirmed the presence of moderate pericarditis with indication of medical treatment, and, taking into consideration the two previous episodes of pericarditis with pericardiocentesis, a suspicion of a systemic disease as a possible etiology was issued.

The neurologic examination confirmed ataxia and the cerebellar syndrome. From neurologic point of view, the skin eruption corroborated
with the neurologic syndrome induced the suspicion of neurofibromatosis. Related to this suspicion, ophthalmologic, dermatologic and cerebral MRI were performed.

The cerebral MRI revealed cerebral, cerebellar, thalamic, and tentorial intraneuraxial lesions with possible granulomatous etiology, as well as a nodular lesion of the upper part of the pituitary stalk and of the hypothalamic infundibulum, with impression on the optical chiasm.

Rheumatologic examination performed in the context of a possible systemic disorder and of the cerebral MRI aspect as well as on the presence of an important inflammatory syndrome, failed to confirm the suspicion of SLE or Wegener granulomatosis based on a normal panel of antibodies (Anti DNA ds antibodies, ANA, pANCA, cANCA, C3, C4), but required skin biopsy.

The suspicion of dermatofibroma was raised by dermatological examination, instead of neurofibromatosis. Skin biopsy was performed and the histopathological result confirmed dermatofibroma (benign fibrous histiocytoma).

Based on the association of skin lesions, lung disorders and on the involvement of hypothalamic-pituitary region and neurodegenerative changes in the cortex, cerebellum and tentorium, on the presence of diabetes mellitus, we took into account another suspicion of diagnosis in this patient: Histiocytosis X. Unfortunately we couldn’t sustain this diagnosis because of the absence of Langerhans cells in the histopathological examination, because of the impossibility of performing cell markers and phenotypes of histiocytic and related disorder and because the patient refused bronchoscopy, bronchoalveolar lavage and bone marrow biopsy which might have provided the histopathological diagnosis.

The patient was treated with antibiotics due to the respiratory symptoms correlated with leukocytosis and inflammatory syndrome, cabergoline 0.25 mg twice a week, desmopresin, 0.1 mg/day, fenofibrate 160 mg/day, Dexametazone 8 mg per day for 5 days. Medrol in dosage of 4 mg per day was tried for 2 weeks but, because of no improvement in patient’s neurologic or respiratory status, corticoid treatment was tapered to zero.

Patient’s evolution under the above mentioned treatment is not satisfactory, even if from endocrinological point of view the patient is compensated, the respiratory function worsens.

We still take in consideration the suspicion of Histiocytosis X but further investigations are necessary: bone marrow biopsy to reveal LCH cells positively stained with antibodies to CD1a, S100 and/or anti-langerin (CD207) or detection of BRAF V 600 mutations. [22]. Several attempts were made to involve the oncologic department in the investigations and treatment procedures, but without the possibility of performing the above mentioned investigations, the patient was not included in chemotherapeutic treatment.

A particularity of our patient is the presence of pericarditis. The main symptoms of our patient (dyspnea with orthopnea, dry cough) are related to the association between pericarditis and pulmonary fibrosis. We found only three other cases of pericarditis in LCH patients in
medical literature: 2 children and one adult. [22, 23, 24]

Conclusions
Histiocytosis X or Langerhans cell histiocytosis is a rare disease with a difficult diagnosis.

Even if the suspicion is based on clinical manifestations, tissular biopsy with immunohistochemical assays or genetic evaluation are required in order to consider the diagnosis.

The association between pericarditis and histiocytosis X is rare and challenges the treatment options.

Treatment requires strong interdisciplinary collaboration between endocrinologist, oncologist, hematologist, pneumologist, orthopedic surgeon and, sometimes, cardiologist, as is in our case.

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Conflict of interests
The authors declare that they have no conflict of interests.

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