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(CASE REPORT)

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A case of non-Langerhans histiocytosis effectively treated with Cobimetinib: A rare case report

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Abstract

non-Langerhans histiocytosis is a group of very rare, clinically heterogeneous diseases, characterized by the proliferation of histiocytes in the connective tissue, it preferentially affects middle-aged men, their classification is difficult, it is based on clinical, histological, immune criteria histochemical and evolutionary.

We report the case of a 58-year-old man with an HIV infection under treatment. The patient initially presented with skin lesions, the skin biopsy was in favor of xanthoma disseminatum, and then the patient presented with bone pain and respiratory symptoms. , the extension assessment and the biopsies confirm the diagnosis of Erdheim-Chester disease with bone, cardiac, aortic and pulmonary involvement and diffuse skin involvement « disseminated xanthoma », the patient was put on Cobimetinib 20 mg / day which resulted in an excellent clinical and radiological response with no reported toxicity.

Cobimetinib is effective and well tolerated in cases of Erdheim-Chester disease; therefore, it could be considered as a good therapeutic option as a monotherapy for patients without BRAF mutation.

Keywords: Erdheim-Chester disease; Histiocytosis; Cobimetinib; Non-Langerhansian

1. Introduction

non-Langerhansian histiocytosis is class C of histiocytic disorders which brings together several subgroups among them we have Erdheim-Chester disease, it is an extremely rare disease affecting middle-aged individuals, it is characterized by the accumulation histiocytes in the connective tissue of the body. As a result, this tissue becomes thick, dense and fibrotic. Different organs can be affected. Without effective treatment, these organs stop functioning.

Although it has been largely underdiagnosed for many decades, many new cases have been reported in recent years. This results above all from the better knowledge of the different aspects of this histiocytosis among pathologists, radiologists and clinicians. Therapeutically, the demonstration of the effectiveness of interferon-α was a major advance. More recently, the BRAFV600E mutation has been detected in more than half of patients with Erdheim-Chester disease. This allowed the use of BRAF inhibitors (vemurafenib) in BRAFV600E mutated patients with severe forms of the disease with spectacular effectiveness.

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2. Presentation of the case

Patient aged 58 with a history of COPD, asthma, Psoriasis, iatrogenic adrenal insufficiency under HYDROCORTISONE 20 mg, thromboembolic disease, HIV-positive patient under antiretroviral treatment since 1997 followed in our department.

In 2018 the patient presented an erythrotic appearance with cutaneous xerosis and yellow papular lesions on the face, on the back he presented diffusely small copper papules, some xanthomatized giving a yellow-orange color, with nodular hyperplasia.

a dermatological opinion was taken which suggests lesions on the face in favor of sebaceous hyperplasia, requiring a skin biopsy with multiple biopsies at the dorsal level while avoiding corticosteroid therapy because an infectious origin was suspected, the anatomopathological analysis which is in favor of non-specific granulomatous dermatitis but whose differential diagnosis such as granuloma annulare, xanthoma or other are mentioned.

Knowing that repeated skin biopsies were inconclusive.

In June 2019: extension of skin lesions to the upper limbs and trunk.

Another skin biopsy was done and it is in favor of xanthelasma according to the dermatologist due to the anti-retroviral treatment.

On 08/09/2019 after the anti-retroviral treatment was incriminated, its treatment based on PREZISTA 600 mg (2 tabs per day), NORVIR 100 mg (2 tabs per day) and CELSENTRI 300 mg (2 tabs per day) was switched by BIKTARVY, 1 single tablet comprising the Co-formulation of 3 molecules (TENOFOVIR ALAFINAMIDE 25 mg, EMTRICITABINE 200 mg and BICTEGRAVIR 50 mg).

This skin rash which persists, with the appearance of stretch marks initially leading to suspicion of Cushing's but nevertheless as a differential diagnosis pathology of collagen or elastin is highly suspicious.

01/24/2020 completion of three biopsies result:

Histological image suggests a predominantly histiocytic dermal infiltrate with multiple xanthogranulomas. Depending on the clinical context and the biological and radiological assessment, this aspect remains compatible with xanthoma disseminatum or Erdheim-chester.

On 07/13/2020 appearance of pain in the joints such as arthromyalgia. Pain in different bony parts such as the tibia, femur, pain predominantly in the lower limbs.

PET-CT was performed on 05/06/2020: this examination highlights damage compatible with non-Langerhans histiocytosis in the long bones and knees in particular. Intense fixation on the PET (lower 1/3 of the femurs and upper 1/3 of the tibias): we see on the scan a heterogeneous bone with small gaps, which do not suggest an acute hematous disease, nor a infection, and compatible with histiocytosis.

Usually, bone histiocytosis is not a problem and progresses locally towards quiescence, therefore no specific treatment.

The diagnosis of non-Langerhans histiocytosis with diffuse skin involvement such as xanthoma disseminatum and bone involvement was made.

An extension assessment was done to research systemic lesions of histiocytosis:

- Search for BRAF mutation on the biopsy shows: an increase in the expression of p ERK in the lesions suggesting possible activation of the MAP kinase pathway. Molecular explorations will be continued.

Since July 2020 AEG with weight loss of 4-5kg, asthenia sweats at night, muscle loss due to bone pain in the knees and right leg shoulder with night waking.

BONE SCINTIGRAPHY ON 02/09/2021: several anomalies of radiotracer fixation with inflammatory component at early stage at the level of the upper and lower mb as well as at the level of the bones of the face compatible with histiocytosis.

Since 2021, the patient was hospitalized several times for progressively worsening dyspnea, which became more and more disabling. A chest CT scan showed: diffuse emphysematous changes, bilateral thickening of the pleura as well as the septa, all compatible with Erdheim Chester pulmonary involvement.

An aortic angioscan was done: on conclusion:

Multiple lesions linked to histiocytosis associating:

- Pulmonary involvement with smooth thickening of the interlobular septa and pleural thickening, particularly of the right pulmonary base.
- Cardiac involvement with thickening of the posterior wall of the right atrium and the internal atrial septum.
- Vascular involvement with parietal thickening of the brachiocephalic artery trunk and, of the left subclavian, of the suprarenal abdominal aorta and of the infrarenal abdominal aorta.
- Bone damage to both femurs.

Genetic analyzes of the biopsy shows : Confirmation of diagnosis of histiocytosis, RNA seq analysis did not reveal a fusion gene., Absence of pathogenic variant, mutation or fusion gene detected in BRAF, MAP2K1, NRAS, KRAS and MAP kinase pathway genes.

A new PET SCANN on 07/13/2022: intensely to strongly hypermetabolic nature of histiocytic bone damage (mainly distal femoral and bilateral tibiofibular) and diffuse pulmonary parenchymal damage. Hypermetabolism extends to the joint areas of the knees and goes up to the periphery of the femurs in the lower part of the thighs hypermetabolic infiltration of the interauricular groove.

In the end, the diagnosis of Erdheim Chester disease with bone, cardiac, aortic and pulmonary involvement and diffuse skin involvement such as xanthoma disseminatum was hold.

In 07/2022: Administration of COBIMETINIB 20mg/day, which gave a clear regression of skin lesions and bone pain, with control PET SCANNER showing: extinction of peripheral pericystic interstitial hypermetabolism of both lungs, partial regression of hypermetabolism periosteal and overall stability of the osteomedullary diaphyso-epiphyseal infiltration of the affected limbs.

Figure 1 Xanthelasma facial before treatment

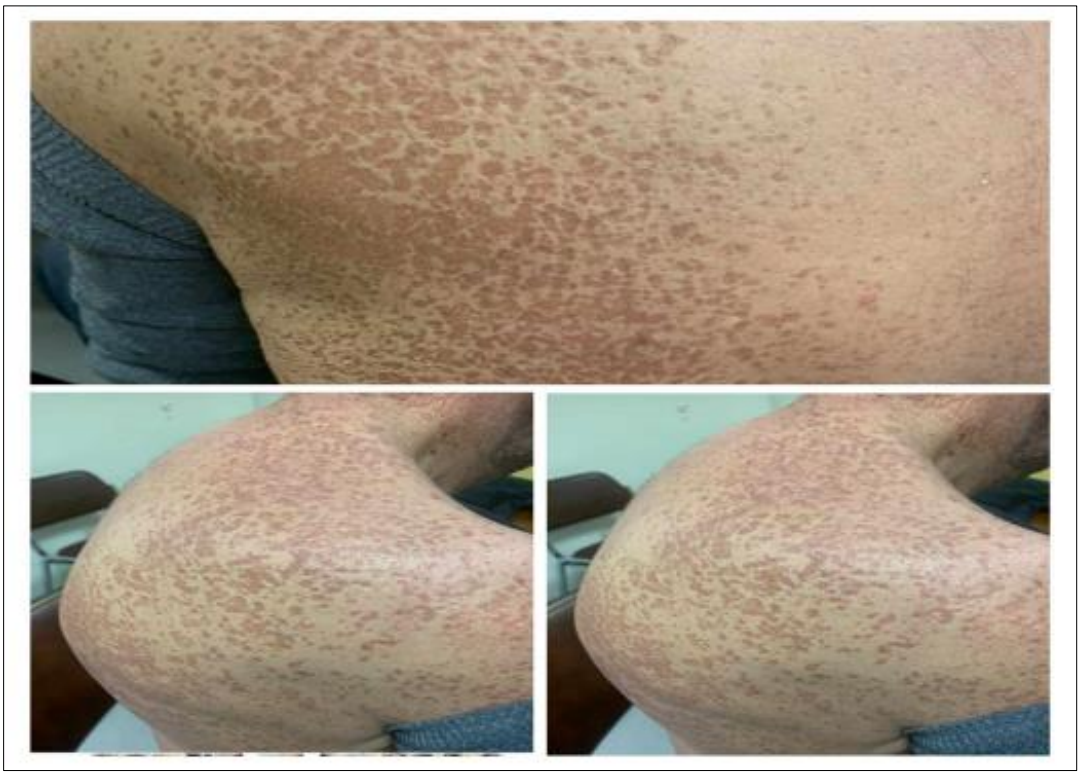

Figure 2 Skin lesions before treatment

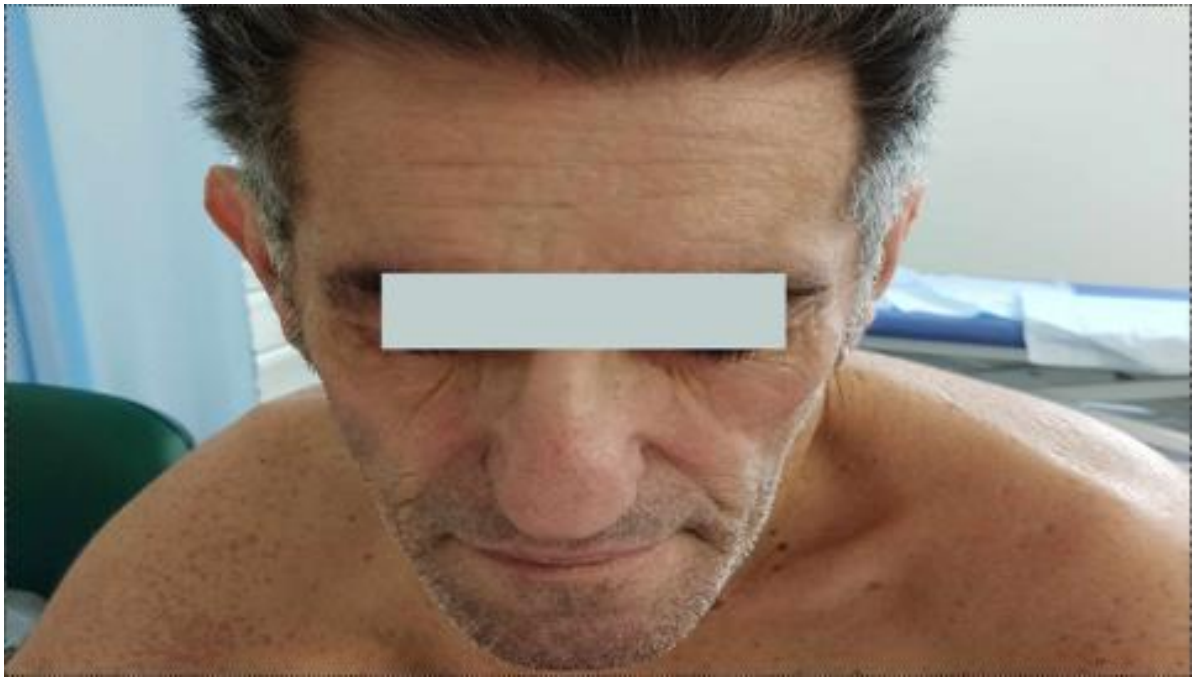

Figure 3 Disappearance of xanthelasma after treatment

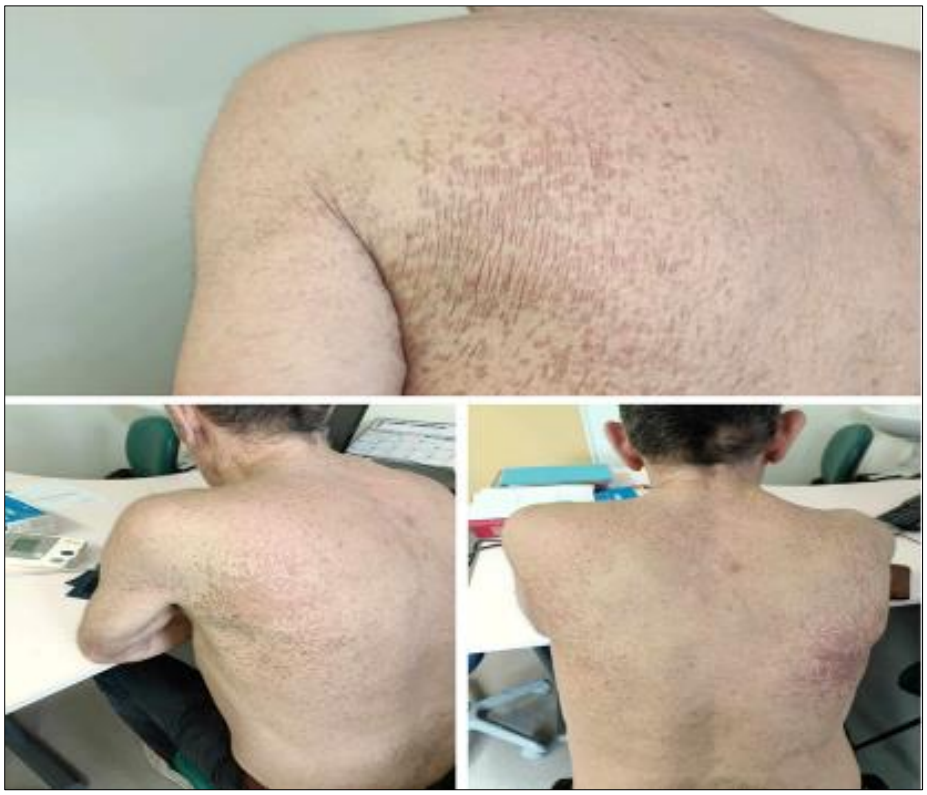

Figure 4 Regression of skin lesions after treatment

3. Discussion

Non-Langerhasian histiocytosis preferentially affects men during the fifth decade, this is a rare disease that can affect many organs of the body, it is characterized by an infiltration of foamy histiocytes, these histiocytes are marked in immunohistochemistry by CD68, CD163 but are negative for CD1a and lagerin (CD207).

In our patient, the disease was initiated by a skin attack of the xanthoma disseminatum type which is present in 25% of patients, the skin attack is manifested by red-brown papulo-nodular papulo-nodules which become increasingly yellow with time. Lesions are often distributed over the eyelids, trunk, face, back and proximal extremities. In the folds, papules often merge into soft plaques.

Secondarily, our patient presented bone damage which is the most common damage of this disease, this damage is almost universal in patients, it is absent only in 4% of cases, the search for subclinical radiological abnormalities must be systematically, it can be demonstrated by standard radiographs which show bilateral and symmetrical cortical osteosclerosis of the metaphyseal-daiphyseal regions of the long bones, or by scintigraphy and PET scan which manifests itself by hyperfixation but the most sensitive to detect this damage this MRI.

In our patient the respiratory symptoms which were increasingly disabling and unexplained by the comorbidities of our patient allowed us to suspect pleuropulmonary involvement which was represented by smooth thickening of the inter lobular septa, pleural thickening and pulmonary fibrosis, the Pleuropulmonary damage is present in 53% of cases, it can vary in severity from asymptomatic damage to chronic respiratory failure, or even episodes of respiratory distress which requires mechanical ventilation.

The other attacks which are rarer and often asymptomatic were detected by a systematic extension assessment which among other things detected the cardiac and aortic involvement despite the fact that our patient had no symptoms on the cardiac and aortic level, histiocytosis this one disease which can affect all organs, upon the discovery of histiocytosis, a complete and extended assessment must be systematic in search of any possible damage.

In recent years, cardiac MRI has allowed a better characterization of cardiac involvement; cardiac MRI performed systematically in 37 confirmed cases of Erdheim-Chester disease made it possible to detect cardiac involvement in 70% of cases.

Retroperitoneal involvement is absent in our patient despite this frequent involvement found in 50% of cases.

Of interest in our case is this spectacular effectiveness without any toxicity of the treatment with COBIMETINIB. Our patient, who does not carry the BRAF mutation, was treated with COBIMETINIB 20 mg/day which made it possible to obtain regression of the skin lesions. and symptoms related to bone and lung damage.

COBIMETINIB is an allosteric, selective and reversible inhibitor that blocks the MAPK pathway by targeting MEK1 and MEK2. Consequently, cobimetinib blocks cell proliferation induced by the MAPK pathway. It is used for the treatment of melanomas and has shown a spectacular effectiveness for the treatment of HNL.

The treatment of HNL is difficult and poorly codified. It is therefore important to report new therapeutic options.

US Food and Drug Administration (FDA) approved the BRAF protein inhibitor vemurafenib for the treatment of histiocytic disorders in 2017, and cobimetinib (Cotellic®) in 2022.

In a study involving 26 patients with different histiocytic disorders conducted by the Memorial Sloan Kettering Cancer Center (MSK), cobimetinib demonstrated robust efficacy in HNL, regardless of the underlying mutation in the MAPK pathway, including BRAF-wt and HN BRAFV600-mutant. The safety of cobimetinib in this patient population was consistent with the known safety profile.

Our patient's remarkable response to cobimetinib further confirms the effectiveness of cobimetinib treatment in patients with histiocytic disorders who do not carry the BRAF mutation.

4. Conclusion

Targeted therapy based on cobimetinib for patients without mutations and in combination with vemurafenib in the presence of mutations can constitute a reference treatment for histiocytic disorders which have remained for a long time without a well-codified treatment.

Compliance with ethical standards

Disclosure of conflict of interest

There are no conflicts to declare.

Statement of ethical approval

The present research work does not contain any studies performed on animals/human subjects by any of the authors.

Statement of informed consent

Informed consent was obtained from the individual participant in this case report.

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