Case Report

Necrobiotic Xanthogranuloma - Case Report and Literature Review -

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ABSTRACT: Necrobiotic xanthogranuloma is a rare type of non-Langerhans histiocytosis, whose main clinical features are the development of red-brown, purplish or yellowish skin papules and nodules, which evolve by forming infiltrated plaques. The periorbital region is the most commonly affected site. Some cases have lesions on the torso or extremities, with no facial involvement. Extracutaneous involvement of the ocular, respiratory, and cardiac tissues have also been described. Most patients have an associated monoclonal gammopathy (IgG k and λ). The treatment is difficult, with progression and recurrence. We present the clinical case of a 65-year-old woman, who was hospitalized for multiple erythematous plaques and placards, with fine squames and telangiectasis on the surface, disseminated within the scalp, ears, trunk, lower limbs; some plaques have a circinate border with reddish-purple, slightly protruding edges and a whitish and erosive atrophic center. The lesions within the scalp are alopecic. The disease began 15 years ago, the patient being diagnosed with Psoriasis vulgaris and treated with dermatocorticoids and Cignolin, with no remarkable results. Paraclinical investigations did not reveal any associated pathologies. Histopathological and immunohistochemical examination confirmed the diagnosis of necrobiotic Xanthogranuloma. The patient was treated with antihistamines, Neuromultivit, Vit E 100mg/day, Oximed spray, Atoderm emollient cream, Neopreol ointment, with slow favorable evolution. The physical examination and laboratory investigations for the diagnosis and surveillance of malignant diseases should be performed on a regular basis in patients with NXG. Our patient had lesions with a course of 15 years, with no development of multiple myeloma or other systemic involvement.

KEYWORDS: *Necrobiotic xanthogranuloma, slow evolution, treatment.*

Introduction

Necrobiotic xanthogranuloma (NXG) is a rare form of non-Langerhans histiocytosis, characterized by the development of red-brown, purplish or yellowish skin papules and nodules, which evolve by forming infiltrated plaques.

The periorbital region is the most commonly affected site.

Extracutaneous involvement of the ocular, respiratory, cardiac tissues have also been described.

Most patients have an associated monoclonal gammopathy (IgG k and λ) [1].

The treatment is difficult, with progression and recurrence [2].

Kossard and Winkelmann first differentiated NXG from xanthomas in 1980 [3].

The mean age of onset is the 6th decade of life, with cases being described among the ages of 17-85 years. There is no sex predilection [4].

The *etiopathogenesis* is not fully elucidated.

One hypothesis refers to the fact that serum immunoglobulins form complexes by binding to lipids and they are stored within the skin, leading to a foreign-body giant cell reaction that leads to NXG lesions [5].

Another hypothesis is that the lesions are the outcome of the macrophage proliferation with affinity for the complement binding fragment (Fc) of the overproduced immunoglobulins.

However, this could be a secondary finding rather than a real cause because paraproteinemia is sometimes absent in NXG [6,7].

Furthermore, there has been research that suggests the hypothesis that activated monocytes, which accumulate lipids, are deposited in the skin and trigger an inflammatory reaction [8].

There were recent remarks supporting the involvement of an infectious element, with a report revealing the presence of Borrelia in 6 out of 7 examined patients [9].

Case Report

We present the clinical case of a 65-year-old woman from a rural area, who was hospitalized for multiple erythematous plaques and placards, with fine squames and telangiectasias on the surface, disseminated within the scalp (Figure 1), ears, trunk (Figure 2), lower limbs (Figure 3); some plaques have a circinate border with reddish-purple, slightly protruding edges and a whitish and erosive atrophic center.

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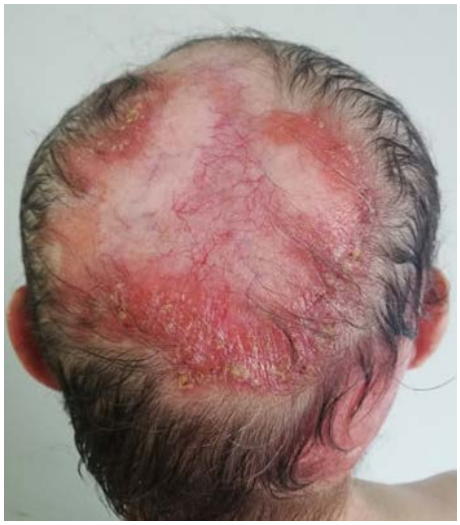

Figure 1. Infiltrated placard with alopecia, telangiectasias and squames located on the scalp.

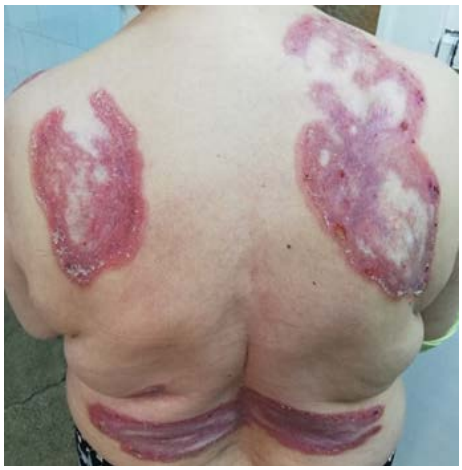

Figure 2. Infiltrated placards with telangiectasias and squames located on the trunk.

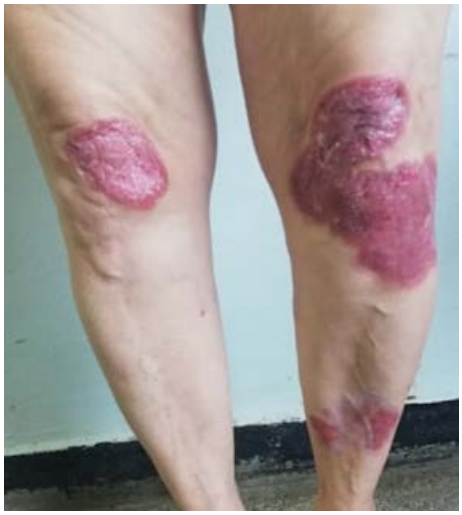

Figure 3. Infiltrated plaques with telangiectasias and squames located on the lower limbs.

The lesions within the scalp are alopecic. The disease began 15 years ago, the patient being diagnosed with Psoriasis vulgaris and treated with dermatocorticoids and Cignolin, with no remarkable results.

The written informed consent of the patient was obtained, who agreed to the publication of this data.

The past medical history revealed uterine fibroids that were operated in 1986, deteriorative organic psychosyndrome (under treatment with Olanzapine 10mg/day for the last 6 years).

After physical examination the patient was deemed as having a phototype II, class I obesity (a body mass index of 31,24), matte, thickened nails with a subungual hyperkeratotic deposit.

Chest X-ray showed no active pleuropulmonary lesions. Heart within normal limits.

Abdominopelvic ultrasound revealed a liver with moderate-diffuse echogenicity. Left lobe of 7cm. Normal gallbladder, bile ducts, pancreas, spleen, kidneys.

Laboratory tests showed normal LDH and autoimmune diseases panel, negative HBs Ag and anti-HCV antibodies; 55.65% (20-55) lymphocytes, 33.04% (45-80) neutrophils, $14.25x10^3$/microL leukocytes. Serum protein electrophoresis was within normal limits.

Under local anesthesia with Xiline 1%, we performed the biopsy of skin lesions from the left knee, right preauricular, subclavicular regions.

The specimens were submitted to the Pathology Laboratory of the Emergency County Hospital of Craiova, where they were processed according to the classical histopathological technique and embedded in paraffin.

Histopathological examination of hematoxylin-eosin stained slides revealed diffuse granulomatous panniculitis and dermatitis, mainly comprised of epithelioid histiocytes and multinucleated giant cells, some with vacuolated cytoplasm, others with a large number of nuclei or with bizarre, triangular shapes, punctuated by collections of lymph and plasma cells; the granulomatous infiltrate was diffusely displayed within the dermis, revealing several areas of necrosis and sclerosis (Figures 4,5).

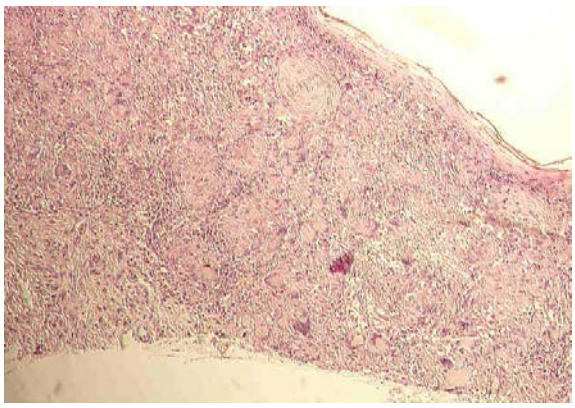

Figure 4. Diffuse granulomatous panniculitis and dermatitis, mainly comprised of epithelioid histiocytes and multinucleated giant cells, some with vacuolated cytoplasm, others with a large number of nuclei or with bizarre, triangular shapes, punctuated by collections of lymph and plasma cells; HEx40.

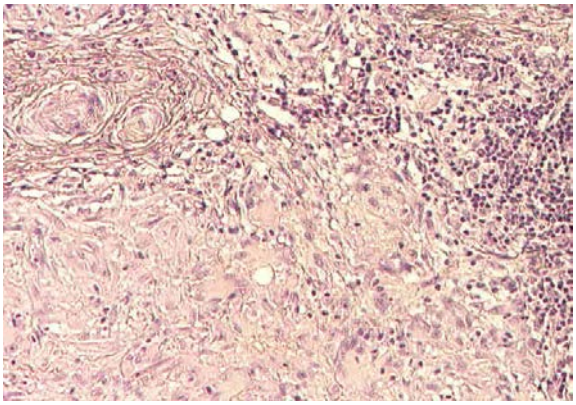

Figure 5. Diffuse granulomatous panniculitis and dermatitis, mainly comprised of epithelioid histiocytes and multinucleated giant cells, some with vacuolated cytoplasm, others with a large number of nuclei or with bizarre, triangular shapes, punctuated by collections of lymphoplasmocytes; x200.

For further description, slides have been processed for immunohistochemistry. Briefly, after antigen retrieval in citrate buffer pH6, endogenous peroxidase blocked in 0.1% water peroxide and unspecific binding sites blocked with normal goat serum.

The primary antibody was added overnight according to the producer description (Novocastra; Leica Biosystems, Medist Life Science S.R.L. Bucharest, Romania), and the next day the signal was detected with a peroxidase-labelled polymer directed against the species of the primary antibodies (Novocastra), then the sections were counterstained with hematoxylin and coverslipped.

Sections have been imaged under a Panthera microscope (Motic Europe, Cabrera de Mar Barcelona, Spain).

Analysis of immunostained slides showed CD3 positive small lymphocytes spread within the granulomatous infiltrate and CD20 lymph cells in the nodular collections of B lymphocytes and plasma cells that punctuate the infiltrate. Plasma cells expressed both kappa and lambda with a ratio of K/λ=4/1 (Figures 6,7,8,9).

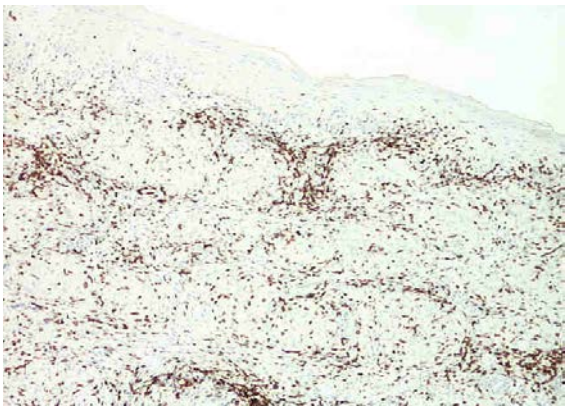

Figure 6. IHC: CD3 stains the small lymphocytes spread within the granulomatous infiltrate; x100.

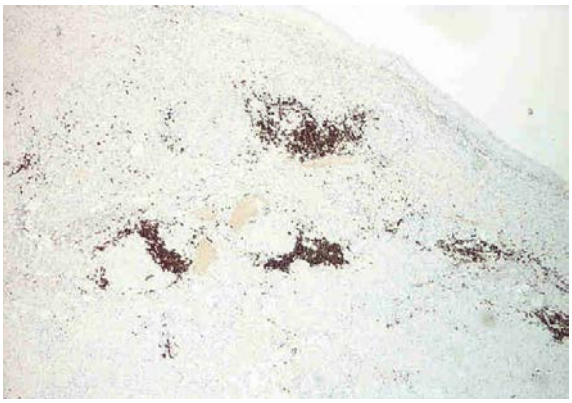

Figure 7. IHC: CD20 highlights the nodular collections of B lymphocytes and plasmocytes that punctuate the infiltrate; x100.

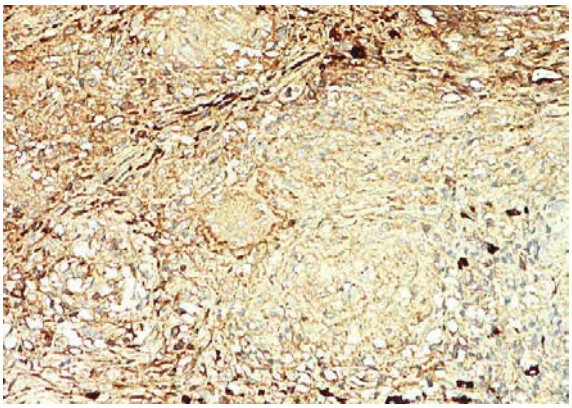

Figure 8. IHC: Kappa chains immuno expression; x200.

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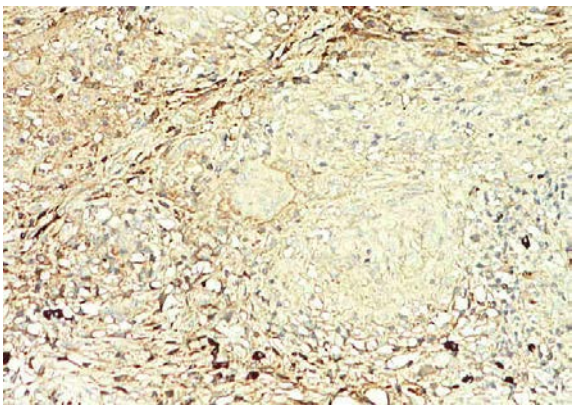

Figure 9: IHC: Lambda expression.

Furthermore, an Alcian blue staining did not show an increased amount of mucin in the dermis.

Based on the clinical, histopathological and immunohistochemical examinations, we stated a diagnosis of ***Necrobiotic xanthogranuloma***.

The patient was treated with antihistamines (Loratadine, Bilastine), Neuromultivit, Vit E 100mg 1 tablet/ day, Oximed spray, Atoderm emollient cream, Neopreol ointment on the lower limb lesions.

Discussion

Clinical features. NXG presents with firm, yellow nodules and plaques of less than 25cm in diameter, which can appear anywhere on the body. Most patients have facial lesions (85%), many of which are located in the periorbital area.

Some cases have lesions on the torso or extremities, with no facial involvement. The plaques are frequently purplish with a yellow, xanthomatous hue and telangiectasias may be present [10].

Periorbital lesions form the most characteristic sign, starting with xanthelasma-like papules that progress to plaques. Ocular manifestations may appear in 50-80% of cases, with conjunctival, corneal, scleral conditions. Other ocular manifestations: diplopia, sclerosis, decreased visual acuity, exophthalmos, blepharoptosis, decreased ocular motility [11].

The lesions may be associated with pruritus or a burning sensation and patients have developed central atrophy and ulceration in 43% of cases.

NXG is seen as a systemic condition. Involvement of the internal organs has been described: heart, lungs, kidneys, intestines, ovaries, larynx, pharynx, skeletal muscles and CNS. Lymphadenopathy is occasionally present.

The involvement of the internal organs may be asymptomatic; the diagnosis being made on autopsy [4,12,13,14,15].

Hematological and lymphoproliferative malignancies in particular, are the most frequently associated systemic conditions that may develop at an interval of 2-4 years after the onset of the skin lesions [16].

Monoclonal gammopathy is present in 80-90% of cases (IgG k in 60% and IgG lambda in 26% of cases; a case with Ig A has also been described). It has been noticed that only 10% of cases will progress to multiple myeloma [11,17,14].

Other associated conditions are Hodgkin's lymphoma, non-Hodgkin's lymphoma, myelodysplastic syndrome, macroglobulinemia, chronic lymphocytic leukemia, cryoglobulinemia and amyloidosis [14].

In a 2009 study (Wood AJ et al) of 17 cases diagnosed with NXG between 1994 and 2007, 11 patients presented with involvement in the orbital region, and the trunk was affected in 8 patients. Twelve patients had monoclonal gammopathy; 3 had multiple myeloma. The histopathological examination was typical in 12 patients. No correlations were found between the clinical and the histopathological aspects [16].

*The positive diagnosis i*s often made on the histopathological examination which reveals: (i) band-shaped granulomatous inflammation comprised of inflammatory cells (foamy histiocytes, lymphocytes, Touton giant cells and foreign-body giant cells) [11]; (ii) most features expand from the middle dermis through panniculitis; (iii) cholesterol clefts occur in necrobiotic focal areas in most cases [18]; (iv) biopsies also show lymphocytic or lymphoplasmacytic nodular aggregates [16].

Laboratory tests may reveal decreased complement levels, anemia, leukopenia.

Differential diagnosis

From a clinical point of view, we took into consideration in our case a differential diagnosis with chronic lupus erythematosus for lesions on the face, psoriasis for lesions on the lower limbs, the chalazodermic form of mycosis fungoides for lesions on the trunk.

From a histopathological point of view, NXG must be differentiated from:

- *sarcoidosis* (a diffuse disposition of the granulomatous inflammation and the presence of several plasma cells);

- *necrobiosis lipoidica* (the presence of bizarre, multinucleate cells and the absence of a

stratified disposition of the granulomatous inflammation);

- *mycosis fungoides* (the infiltrate is mainly a granulomatous one instead of being lymphoid, while secondarily being associated with small lymphocytes and plasma cells);

- *mycobacterial infections*.

Course and prognosis. NXG has a chronic, progressive, indolent course. The prognosis depends on the seriousness of the extracutaneous manifestations, the presence of hematological malignancies and the complications of the skin lesions [13,19,20].

Multiple myeloma that develops in patients with NXG seems to exhibit a relatively benign behavior. Ugurlu et al. stated that 90-100% of patients with multiple myeloma and NXG may survive for at least 10-15 years [4,11,12].

Treatment. There is no consensus regarding the optimal therapy.

Wood et al. described chemotherapy as the most common treatment and noted the effectiveness of chlorambucil and corticosteroids in small doses, alone or in combination [21-25].

Other treatments described were: cyclophosphamide [26], melphalan [27,28], azathioprine in combination with corticosteroids [29], thalidomide [30], alpha-interferon [31], IV Ig.

The treatment leads to the remission of paraproteinemia and skin lesions, but it cannot prevent the course toward multiple myeloma.

Elners et al. showed that intralesional injections of triamcinolone acetonide were effective for orbital NXG in adults [32].

Surgical excision may be beneficial in localized skin lesions, excluding lesions in the periorbital region due to the high recurrence rate, stimulation of lesion activity and forming of scars, followed by eyelid retraction.

Cryotherapy and radiotherapy yielded no successful outcomes.

Thalidomide may be an interesting option for intractable skin lesions.

Conclusions

The physical examination and laboratory investigations for the diagnosis and surveillance of malignant diseases should be performed on a regular basis in patients with NXG.

Our patient had lesions with a course of 15 years, with no development of multiple myeloma or other systemic involvement.

Conflict of interests

None to declare.

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