Interstitial Granulomatous Dermatitis due to a Rare Myeloproliferative Neoplasia

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Abstract
Interstitial granulomatous dermatitis (IGD) was first described in 1993 by Ackerman as a cutaneous reactive disease in patients with arthritis. Since then, numerous cases associated with different hematological and rheumatic disorders have been reported. IGD is a polymorphic entity that usually involves the upper part of the trunk. Histologically, it is defined as a diffuse dermal histiocytic infiltrate of different densities surrounded by fragmented collagen. We report the case of a 56-year-old man with pruritic papules affecting neck, proximal arms and thorax associated with weight loss and chronic fatigue for six months. Two punch biopsies were taken and the specimens showed lymphohistiocytic interstitial infiltrates with fragmented collagen and elastic fibers in dermis. IGD was diagnosed as first manifestation of a rare chronic myeloproliferative hematologic disorder (cMPD) with rearrangement of beta-receptor for platelet-derived growth factor (PDGFRB). After two months of imatinib, lesions regressed completely.

Key Words: Hematological disorders, imatinib, interstitial granulomatous dermatitis

Introduction
IGD was first described in 1993 by Ackerman as a cutaneous reactive disease in patients with arthritis. Since then, numerous cases associated to different hematological and rheumatic disorders have been reported. IGD is a polymorphic entity that requires a correct histopathological correlation. We report IGD case as a first manifestation of a rare cMPD disorder with rearrangement of beta-receptor for platelet-derived growth factor (PDGFRB).

Case Report
A 56 year-old male was referred to our Dermatology Department because of pruritic papules resistant to topical corticosteroids over the trunk for 6 months. He had also complaints of weight loss and chronic fatigue. Physical examination revealed symmetric, elastic, yellowish erythematous papules affecting neck and the proximal areas of arms and thorax [Figure 1]. Peripheral lymphadenopathies were not present. Blood test revealed leukocytosis (white cell count, 38,830/mm³; normal range, 4000–11,000), and b2-microglobulinemia (5.9 mg/dl; normal range, 0–2.5 mg/dl). Computed tomography scan reported fat infiltration in the abdominal area, pericelal adenopathies, and hepatosplenomegaly. The blood smear detected myelemia, immature granulocytes in peripheral blood, and cytogenetic of the bone marrow biopsy confirmed clonal rearrangement of beta-receptor for platelet-derived growth factor (PDGFRB) (5q32-q33). Two punch biopsies were taken and the specimens showed lymphohistiocytic interstitial infiltrates (CD68+, S100−, and CD1a−), with isolated neutrophils and eosinophils, that fragmented the collagen and elastic fibers in dermis [Figures 2a and b]. The patient was put on imatinib treatment (100 mg/24 h orally), and after 2 months, both systemic and cutaneous lesions regressed completely [Figure 3].

Discussion
IGD is a reactive cutaneous disease that has been associated with multiple diseases. Most of the cases have

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been described in the context of rheumatoid arthritis and seronegative arthritis – known as Ackerman syndrome. It has been also related to inflammatory autoimmune diseases and solid organ neoplasms. Finally, it has been reported in isolated cases of diabetes, dyslipidemia, pulmonary silicosis, and infections such as borreliosis or coccidioidomycosis.\(^1,2\)

Histopathologically, it is defined by a diffuse dermal histiocytic infiltrate of different densities surrounded by fragmented collagen. The inflammatory infiltrate is mainly made up of CD68+ histiocytes. Occasional neutrophils and eosinophils, as well as occasional elastic fiber fragmentation correlating with a cutis laxa-like phenotype, may be observed. Usually, there is no vasculitis – more typical of palisaded neutrophilic granulomatous dermatitis – and there is no mucin deposit, typical of interstitial annular granuloma. In the histological differential diagnosis, we must also include interstitial granulomatous drug reaction. In this case, the most significant are vacuolar interface reaction, dyskeratotic keratinocytes, and intense tissue eosinophilia. Overlap of histological findings is common, leading to confusion. For this reason, some authors propose to include them in a common term called “reactive granulomatous dermatitis.”\(^1\)

IGD manifests as erythematous papules or plaques distributed symmetrically in lateral aspects of the trunk and the proximal inner aspects of the limbs. The “rope sign” is considered pathognomonic, although only 9% of the cases presented with it. Erythematous subcutaneous lines or skin-colored cords that extend down on trunk characterize it. Many of them are asymptomatic or slightly symptomatic with mild itching and burning.\(^2\)

The pathogenesis is unknown. Some authors attribute it to an immune-mediated hypersensitivity mechanism involving macrophage activation.\(^3\)

IGD’s evolution is uncertain. From the published series, a complete response is observed in 66% after a period of 3 months to 3 years. In 30% of cases, the disease persists presenting a chronic-relapsing course.\(^3\) Moreover, there is no well-defined treatment. Spontaneous remission is also possible, although in some cases it has shown a paraneoplastic-like behavior with therapeutic resistance in agreement with the tumor progression.\(^3\)

To date, only 6% of cases published are associated with hematological disorders [Table 1].\(^2\) As far as we know, this is the first time in which the association of IGD to myeloproliferative neoplasm with rearrangement of PDGFRB is described. This disorder is included in the category of myeloid neoplasms associated with PDGFRB rearrangement of the WHO classification of 2008.

Although clinical and hematological findings are heterogeneous, it is common to find leukocytosis, and eosinophilia, although it may be absent in a subset of cases.\(^2\)

The result of the chromosomal translocations, as the mutation found in our case (5q32-q33), has opened the door to the treatment with imatinib. Imatinib is an inhibitor of tyrosine kinase approved for chronic myeloid leukemia and gastrointestinal stromal tumors. However, a good response has been demonstrated in cases of MPN with PDGFRB rearrangements acting as target treatment. In the present case, the patient was treated with
imatinib and after two months of therapy both systemic and cutaneous lesions subsided.

Conclusion
If an IGD is diagnosed, it is necessary to perform a screening for systemic diseases, especially hematological diseases.

Although a specific treatment is still unknown, it is important to control the underlying disease since it is sometimes the key to its management.

Table 1: Review of interstitial granulomatous dermatitis associated with hematological disorders

| Classification | Baseline disease | Reference | Treatment | Base disease response | IGD response |
|---------------|------------------|-----------|-----------|-----------------------|--------------|
| No-neoplastic hematological disorder | | | | | |
| Hematological disorder | Anemia | Peroni et al.[2] | Systemic corticosteroids | Unknown | RP, 6 months |
| | Autoimmune thrombocytopenia | Peroni et al.[2] | Systemic corticosteroids | Unknown | RC, 6 months |
| | Leukopenia | Peroni et al.[2] | Topical corticosteroids | Unknown | RC in 15 days (then recurrent skin disease controlled with topical steroids) |
| | Hemolytic anemia | Tomasini and Pippione[4] | Alpha blockers | Unknown | RC, 3 months |
| Hematological disorder | Acute leukemia | Swing et al.[3] | Polychemotherapy + antibiotic + 5-azacytidine | RC, time not determined | NR |
| | MDS | Patsinakidis et al.[6] | No treatment | No (evolution to acute myeloid leukemia at 3 years) | RS, 1 month |
| | Lymphoproliferative syndrome | Anaplastic large cell lymphoma | Choi et al.[8] | Cyclophosphamide + doxorubicin + vincristine + etoposide | RC, time not determined | RC, time not determined |
| | | Diffuse large B-cell lymphoma | Michailidou et al.[9] | Exacerbation after administration of anakinra for baseline disease | | |
| | | Hodgkin’s lymphoma | Peroni et al.[2] | Systemic corticosteroids + methotrexate | Unknown | RC, 6 months |
| Monoclonal gammopathy | Gammopathy IgA | Peroni et al.[2] | No treatment | Unknown | RS, 3 months |
| | Myeloma | Thompson et al.[10] | Bisphosphonates | | RC, “shortly” |
| | cMPS | Lozano-Masdemont et al.[7] | Systemic corticosteroids + hydroxyurea + acetylsalicylic acid | Unknown | RP, recurrent skin disease |
| | cMPS (current case) | Imatinib | | | |

RP: Partial response, RC: Complete response, RS: Spontaneous resolution, NR: No response, MDS: Myelodysplastic syndrome, cMPS: Chronic myeloproliferative syndrome, IGD: Interstitial granulomatous dermatitis

Declaration of patient consent
The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest
There are no conflicts of interest.

What is new?
The association of IGD with a rare myeloproliferative hematologic disorder (cMPS) with rearrangement of beta-receptor platelet derived growth factor (PDGFRB) has not been reported earlier.

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