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Atypical presentation of Cryoglobulinemia: Case study

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ABSTRACT

Cryoglobulinemia is the presence of immunoglobulins (Igs) that precipitate at low temperatures in serum. cryoglobulinemia is which classified by the components of the cryoprecipitate into 3 types; type I, isolated monoclonal immunoglobulins; type II, a monoclonal component, usually immunoglobulin M (IgM), possessing activity toward polyclonal immunoglobulins, usually immunoglobulin G (IgG); and type III, polyclonal immunoglobulins of more than one isotype. This classification provided a framework for clinical correlations. The vast number of varied conditions associated with the production of cryoglobulins can be roughly classified into three categories: chronic hepatitis C and other infections, autoimmune diseases, and B-cell lymphoid malignancies. Purpura is the main clinical manifestation of cryoglobulinemia being reported in 55% to 100% of patients. The incidence is higher in patients with type II and III cryoglobulinemia rather in those with type I. In this work a 74-year-old female patient complained from atypical presentation of cryoglobulinemic vasculitis confirmed with histopathology, that led to the discovery of relapsing non-Hodgkin lymphoma in apparently healthy individual.

Keywords: Cryoglobulinemia, Lymphoma, Atypical presentation.

INTRODUCTION

Cryoglobulinemia is the presence of immunoglobulins (Igs) that precipitate at low temperatures in serum (Perez-Alamino and Luis, 2014). In type I cryoglobulinemia, most clinical manifestations are secondary to hyper viscosity syndrome, with cryoglobulin precipitation and vascular occlusion. Mixed type II–III cryoglobulins are associated with clinical manifestations typical for small–medium vessel vasculitis. Skin is the most frequently involved organ, presenting as palpable purpura, ulcers, hemorrhagic crust (Kluger et al., 2011).

B-cell lymphoproliferative disorders are the major cause of cryoglobulinemia associated with malignancy and the treatment approach in patients with cryoglobulinemia should take into consideration the entity of symptoms as no laboratory marker is strictly correlates with disease activity. While no initial treatment is required in asymptomatic patients, yet in symptomatic disease therapy individual patients should be adapted according to the severity of clinical symptoms and to the underlying disorder. The course and outcome of cryoglobulinemia varies considerably across individuals. The prognosis depends chiefly on the severity of the organ involvement and more specifically of the renal, gastrointestinal, cardiac, and central

nervous system manifestations (Desbois *et al*., 2019)

Case Presentation

Patient:

Sex: female

Age: 74 years old

Diagnosis:

- Since 2010, she complained from sever weight loss within two months, and sever arthralgia with axillary mass, biopsy was taken from the axillary mass and was diagnosed as non-Hodgkin lymphoma. Positron Emission Tomography (PET) scan indicated other masses at abdomen and chest.
- She was treated by rituximab (MabThera) and received 12 doses in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) chemotherapy till 2017 and the patient was cured.
- In August 2020 she presented to primary health care with unilateral purpuric ecchymotic patches and few small hemorrhagic crusts at the upper left side of face including eye and frontotemporal portion of scalp and nose, her left eye was closed due to sever inflammation. She was diagnosed as ophthalmic herpes zoster and was treated by valacyclovir one gram three times per day for a week without improvement and the lesion became progressive and after 2 weeks she took acyclovir intravenous (20 mg/kg max 800 mg) three times per day for a week) without any improvement then was diagnosed as cellulitis and was treated by oral and parental antibiotics without improvement, but the lesions became sharply demarcated patches, and extended to the other side of face, the neck and upper extremities showed purpuric and eczematized skin lesions. All lesions were moderately painful and the trunk and lower extremities were totally free (Fig. 1 A, B, C, D, E).
- She also suffered from arthralgia of the knees and heels.
- She was hospitalized and sought dermatological advice, and her differential diagnosis was angiosarcoma, systemic amyloidosis and erytheploid metastases.
- Two punch skin biopsies (3 mm each) were taken: the first one was from hemorrhagic patch on the face. The examination revealed an intact epidermal covering display focal vascular interface change. The dermis showed multiple thick-walled blood vessels surrounded by homogenous eosinophilic material and associated with prominent RBCs extravasation, some of the affected vessels showed neutrophil rich inflammatory cell infiltration that permeate the wall of the blood vessel forming focal vasculitis changes. Other vessels showed endothelial proliferation and focal occlusion of their lumina by homogeneous eosinophilic material, also the dermis showed edema and disintegration of the elastic fibers (Fig. 2A, B, C).

  The second biopsy was taken from the erythematous scaly patch on the right arm. The histopathological examination revealed similar changes to specimen 1 (Fig. 2 D, E, F).
- Immunofluorescence study for Thioflavin -T dye and Congo red stain were done and revealed mild positive fluorescence of eosinophilic deposits for Thioflavin -T dye, while Congo red was negative under polarized light, excluding the possibility of cutaneous amyloidosis.

- Periodic acid Schiff (PAS) stain was done and revealed positive staining of the eosinophilic deposits, suggesting cryoglobulinemic deposits (Murph *et al*., 2019).
- The histopathological features were highly suggestive of cryoglobulinemic vasculitis.

Direct immunofluorescent was not done due to lack of material, but we confirmed the diagnosis by histopathology, radiologically, laboratory with clinical correlation.

The skin lesions persisted all this period and became very painful. The patient was treated with dexamethasone 8 mg daily to control the inflammation until the oncologist put the plan of treatment, after few days the inflammation of the face gradually subset and the purpuric, ecchymotic patches were improved (Fig. 1F).

Laboratory findings:

These revealed an inflammatory syndrome with elevated C-reactive protein (127 mg/L). Erythrocyte Sedimentation Rate (ESR) was (127 mm nr up to 20), elevated Alkaline Phosphatase (223 U/L nr 35-105), elevated serum B2 Microglobulin was (6.3 μg/ ml nr 0.8-2.2), positive serum cryoglobulin, low complement 4 and complement 3 was normal. There were negative rheumatoid factor activity, antiphospholipid antibodies, hepatitis c virus, hepatitis B virus and antibodies, anti-nuclear antibodies and HIV serology.

Radiological findings:

The results of (PET/CT) study indicated newly developed metabolically active small bilateral deep-cervical, upper abdominal and bilateral inguinal lymph nodes with diffuse splenic hyperactivity and peri pancreatic lymph nodes are noted. When compared this study to previously done as follow up in 2019, relapsing lymphoma was suggested (Fig. 2G).

On the other hand, biopsy taken from inguinal lymph nodes confirmed the diagnosis of relapsing lymphoma.

DISCUSSION

Although lesions on the leg were common in all types of cryoglubinemia especially cryoglobulinemic vasculitis (Dammacco *et al*., 2011), the current study case had atypical manifestation at head and upper extremities only. Although, cryoglubinemia immunoglobulins precipitate occurs at low temperatures, yet our case had her skin manifestations at summer which may be related to the widespread and extensive use of air conditions. So, dermatologist should be aware about atypical presentations and atypical situations of cryoglobulinemia as skin lesions may be the first symptoms of systemic malignant diseases.

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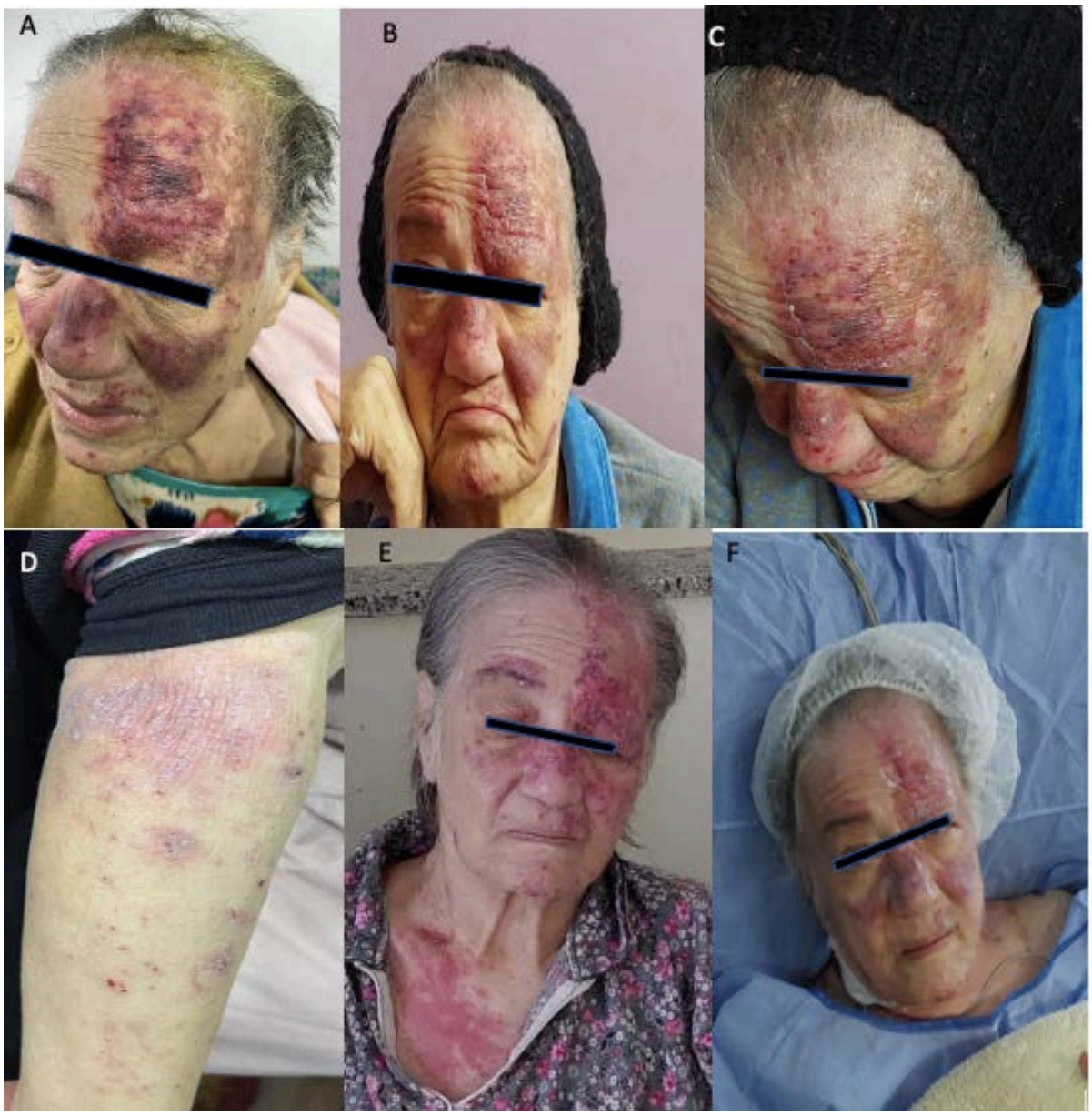

Fig. 1. Photomicrogrphs of a 74-year-old female patient complained from bilateral a symmetrical purpuric ecchymotic patches and few small hemorrhagic crusts (A, B, C, E) at the upper left side of face including eyelid and frontotemporal portion of scalp, nose, cheeks and upper chest, her left eye was closed from the sever inflammation.
(D) Left arm showed purpuric and eczymatized skin lesions.
(F) After few days of treatment, the inflammation of the face gradually subset and the purpuric, ecchymotic patches improved and the closed eye was opened.

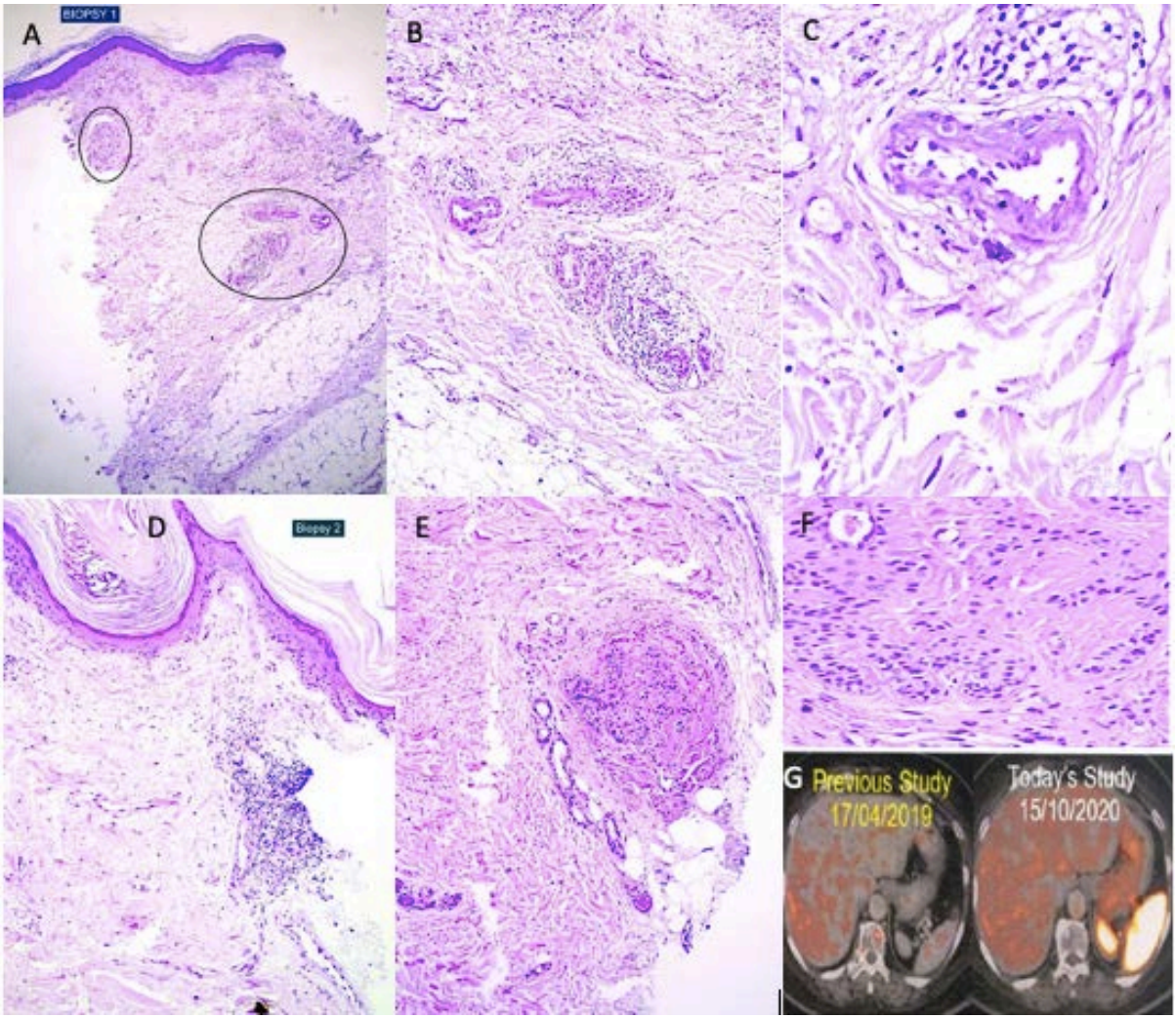

Fig. 2 (A, B, C) Section in biopsy (1) taken from hemorrhagic patch on the face, showing an intact epidermal covering display focal vascular interface change. The dermis showed multiple thick-walled blood vessels surrounded by homogenous eosinophilic material and associated with prominent RBCs extravasation, some of the affected vessels showed neutrophil rich inflammatory cell infiltration that permeate the wall of the blood vessel forming focal vasculitis changes.
(D, E, F) section in biopsy (2) from erythematous scaly patch on the right arm, showing as biopsy (1) in addition, there was hyperkeratosis with irregular thickening of the epidermis. The homogeneous eosinophilic deposits were also seen around the eccrine glands.
(G) A positron emission tomography (PET) scan showed diffuse splenic hyperactivity and presence of peri pancreatic lymph nodes, the largest measured 1.2 cm and achieved 5.5 SUV max at the former one. When compared this study to previously done as follow up in 2019, relapsing lymphoma was suggested.

عرض غير نمطي للجلوبيولين البردي في الدم: دراسة حالة

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المستخلص

الجلوبيولين البردي في الدم هو وجود الجلوبيولين المناعي (Igs) الذي يترسب عند درجات حرارة منخفضة في المصل. الجلوبولينات البردية في الدم هي التي تصنف حسب مكونات الراسب البردي إلى ٣ أنواع؛ النوع الأول، الجلوبيولين المناعي وحيدة النسيلة المعزولة؛ النوع الثاني، مكون وحيد النسيلة، عادة الجلوبولين المناعي M (IgM))، يمتلك نشاط تجاه الجلوبولين المناعي متعدد النسيلة، عادة الجلوبولين المناعي G (IgG))؛ والنوع الثالث، الجلوبيولين المناعي متعدد النسيلة الذي يحتوي على أكثر من نظير واحد. يقدم هذا التصنيف إطارًا للارتباطات السريرية. يمكن تصنيف العدد الهائل من الحالات المتنوعة المرتبطة بإنتاج الجلوبيولينات البردية تقريبًا إلى ثلاث فئات: التهاب الكبد الوبائي المزمن وغيره من أنواع العدوى، وأمراض المناعة الذاتية، والأورام الخبيثة في الخلايا البائية. الفرفرية هي المظهر السريري الرئيسي لمرض الجلوبيولين البردي الذي يتم الإبلاغ عنه في ٥٥٪ إلى ١٠٠٪ من المرضى. تكون نسبة الإصابة أعلى عند المرضى الذين يعانون من النوع الثاني والثالث من الجلوبولينات البردية في الدم مقارنةً بالنوع الأول. في هذه الدراسة اشتكت مريضة تبلغ من العمر ٧٤ عامًا من عرض غير نمطي لالتهاب الأوعية الدموية بالجلوبيولين البردي الذي تم تأكيده من خلال التشريح المرضي، مما أدى إلى اكتشاف سرطان الغدد الليمفاوية اللاهودجكين الانتكاسي لدى فرد يبدو سليمًا.