DIAGNOSIS AND TREATMENT DIFFICULTIES IN A MULTIPLE RELAPSING CASE OF ERYTHEMA NODOSUM

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Summary

Erythema nodosum (EN) is an inflammatory reaction that involves the skin and subcutaneous fat, presenting as tender, erythematous nodules on both shins. It is associated with infection, drug intake, inflammatory conditions, malignancy, or pregnancy. In most cases, it is an acute process with self-limited clinical evolution. Therapeutic options include extended bed rest, NSAIDs, colchicine, or oral potassium iodide for pain management. Systemic corticosteroids may be prescribed in cases with severe symptoms, but only if infection, sepsis, and malignancy have been ruled out.

We present the case of a 26-years old female diagnosed with relapsing erythema nodosum. In this case, the Covid-19 infection might be the first trigger of EN, subsequently maintained by other infectious agents. Diagnosis and treatment difficulties were due to Covid-19 epidemiological context and lack of gastrointestinal and pharyngeal symptoms.

This paper is the first publication from Romania, presenting an association between Covid-19 infection and a relapsing EN case in a young patient without other diseases.

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Introduction

Erythema nodosum (EN) is an acute inflammatory reaction of the skin and subcutaneous fat in response to numerous stimuli. The evidence supports the involvement of type IV delayed hypersensitivity. [1-3]

Characteristic findings in a nodule biopsy are septal panniculitis without fat necrosis and scattered radial Miescher granulomas within the connective tissue septa. Early in the course, neutrophilic inflammation is common, but lymphocytes, histiocytes, and giant cells predominate in later stages. Vessels show endothelial cell swelling, inflammation in the vascular walls, and hemorrhage. [4-5]

The hallmark of erythema nodosum is the sudden onset of one or more tender, symmetric, erythematous nodules, located on the the lower extremities' ventral aspect and more rarely on the arms, trunk, head, and neck. Initially, the nodules are firm, but in evolution they become more fluctuant, healing completely in one-two months. As they are healing, they may assume an ecchymotic appearance. This bruise-like transformation, sometimes known as 'erythema contusiformis', is characteristic of EN and can be helpful for a retrospective diagnosis. Ulceration, suppuration, and scarring do not occur, but residual hyperpigmentation can persist for weeks to months. [1,3,6]

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The female: male ratio varies between 3- 7: 1 and occurs most frequently in persons between 20-30years.[1,7,8]

General overview

The associated conditions can be divided into three categories: drug exposures, infections, and systemic diseases (frequently inflammatory disorders). The drugs most commonly associated are antibiotics and oral contraceptives.

The infectious agents associated with EN tend primarily to affect the respiratory or gastrointestinal tract and are most often bacterial or fungal. A variety of infectious agents have been associated including streptococcal infections, bacterial gastroenteritis, Chlamydia infections, Mycoplasma infections, Yersinia enterocolitica, hepatitis B, tuberculosis, Bartonella henselae, leptospirosis, toxoplasmosis, Q fever, salmonellosis, Campylobacter spp., tularemia. Also, deep fungal infection has been associated with erythema nodosum, particularly coccidioidomycosis, blastomycosis, and histoplasmosis, [3,4,6]

Non-infectious inflammatory conditions, such as sarcoidosis, inflammatory bowel disease, and rheumatological and autoimmune diseases such as systemic Lupus erythematosus, Behçet disease, reactive arthritis, may trigger the reaction, pregnancy, and rarely malignancy such as leukemia and lymphoma. The causative factor could not be determined in 55% of patients. [8] [2-6,9]

In the light of previous events, two EN cases associated with Covid-19 infection were described, both with favorable evolution. [10-11] However, EN was not listed among cutaneous manifestations found in Covid-19 infection.[12]

One to three weeks before the onset, regardless of the etiology, a prodrome occurs. Specific symptoms may include weight loss, malaise, low-grade fever, myalgia, and arthralgia. [1,2,4]

Clinical differential diagnosis must be made with other diseases that may present as tender erythematous subcutaneous nodules. The most frequent are erythema induratum of Bazin (Mycobacterium tuberculosis), nodular vasculitis, cutaneous polyarteritis nodosa [13]. Vasculitis and zones of fat necrosis are absent in EN and frequent in erythema induratum. In polyarteritis nodosa, medium-sized arteries are affected with necrosis of the walls. Nodular vasculitis has mainly lymphocytic infiltration with fibrous thickening and obliteration of vascular lumens and fat necrosis.[14]

For the diagnosis, some paraclinical investigations must be undertaken, like complete blood count, erythrocyte sedimentation rate, and C-reactive protein levels, evaluation of streptococcal infection using throat swab culture, antistreptococcal O titers, chest radiography to exclude sarcoidosis or tuberculosis, evaluation for inflammatory bowel disease for patients with gastrointestinal symptoms. When the diagnosis is in doubt, an excisional biopsy should be obtained. [1,15]

EN is usually an acute process, the clinical evolution is self-limited and spontaneously resolves in 4-6 weeks without any sequelae. In some cases, Chronic or recurrent EN has been described using terms such as chronic EN, EN migrans, subacute nodular migratory panniculitis (Vilanova disease), or septal granulomatous panniculitis. Most frequently occurs in middle-aged women and may be present for several years.[4]

The cutaneous lesions' pathophysiology is not well understood, but evidence suggests that immunoglobulins and complement are present in blood vessels. The localization on lower limbs may be related to hemodynamic factors with deposition of immune complexes in those vessels [16]

Therapy addresses the underlying cause when known. If idiopathic, treatment is mainly symptomatic. Pain can be managed with nonsteroidal anti-inflammatory drugs. Oral potassium iodide in a 400-900mg dosage per day for one month is a therapeutic option for pain if administrated at the onset. If malignancy, infection risk of bacterial dissemination, and sepsis have been excluded, systemic steroids can be a therapeutic option. Treatment also may be tailored to disease-specific regimens.[1]

Case report

We present a case of a 26-year-old woman admitted to the infectious diseases department with a positive Covid-19 test and a recent history of headache, fatigue, nasal congestion, and anosmia. The patient noticed the presence of an erythematous, painful nodule ten days before admission to the hospital, but ignored it.

She was treated with a combination of hydroxychloroquine 400 mg per day and lopinavir/ritonavir 400/100 mg twice daily according to the local hospital Covid-19 protocol for 2 days, but due to severe dyspepsia, the treatment was stopped.

The patient was discharged positive for Covid-19 and isolated at home. Two days later she noticed the appearance of four painful erythematous nodules, on the anterior shins of both lower limbs accompanied by arthralgia, myalgia, without fever (fig. 1). She addressed the Dermatology department and the diagnosis via telemedicine was erythema nodosum. In this case, the first nodule appeared in the Covid-19 infection prodromal period with subsequent appearance of the rest of the nodules.

Treatment started with Methylprednisolone 32mg a day, lowering the dose within 12 days (RT-PCR for Covid-19 still positive), and local treatment with topical anti-inflammatory and heparin. The evolution was favorable in the short term with the remission of pain and nodules, but in evolution, two mild relapses occurred and were treated with COX2 NSAIDs without resolution, which led to the resumption of Methylprednisolone 32 mg a day treatment with slowly lowering the dose (fig. 2). Also, after 4 weeks the test for Covid-19 was negative.

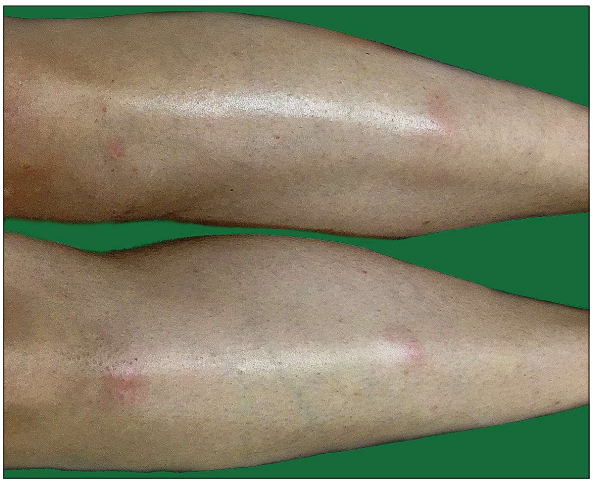

Figure 1. Onset of erythema nodosum lesions.

Figure 2. Erythema nodosum lesions at one month after onset.

The laboratory findings (at the beginning) showed normal fibrinogen, elevated erythrocyte sedimentation rate, anemia, lymphocytopenia, leucopenia with neutropenia. Chest radiography showed interstitial inflammation with no other abnormalities. Antistreptolysine antibodies were undetectable.

After three months, due to multiple relapsing disease, the investigation panel was extended, including an infectious panel with viral B and C hepatitis workup, nasal, pharyngeal, and vaginal swabs culture, Helicobacter pylori antigen, urinalysis, urine and stool culture for bacteria, fungus and parasites and lues screening (fig. 3).

Figure 3. Erythema nodosum nodules with bruise-like appearance (at 3 months after onset).

Angiotensin-converting enzyme and Quanti-FERON Test were normal and sarcoidosis and tuberculosis were excluded. Thyroid panel testing for ATPO, Free T4, and TSH were normal. Complement C3, C4, antinuclear antibodies, rheumatoid factor, lupus cells, cryoglobulins and cryofibrinogen, immunoglobulins IgG and IgA were normal, except for IgM (252 mg/dl). Anti-Covid-19 antibodies at four months after first symptoms were positive for both IgM and IgG.

Further results showed normal inflammation tests, lymphocytosis, monocytosis, low iron deposits (low ferritin), stool culture positive for Pseudomonas aeruginosa, and nasal and pharyngeal swabs for Staphylococcus aureus. Treatment was directed by antibiogram which showed sensibility, for both Pseudomonas aeruginosa and Staphylococcus aureus, for Ciprofloxacin. It was prescribed Ciprofloxacin 1g per day, Fluconazole 150 mg every 2 days, probiotic and intranasal application with Fusidic acid in association with a low corticosteroid dose, fact that conducted to rapid remission of nodules (fig. 4).

Discussions

In this particular case, the appearance of nodules overlapped with the Covid-19 prodromal period with an evolution of over seven months of relapsing disease.

Relapses that appeared immediately after Methylprednisolone discontinuance may be due to prolonged antigenic stimulation (28 days) and the presence of anti-Covid-19 IgM antibodies. Also, the lack of angina and gastrointestinal symptoms suggesting another infectious trigger, made this case difficult.

It is important to extend the investigation panel, inclusively searching for occult infectious agents when an erythema nodosum diagnosis is concluded. It cannot be determined which of the infectious agents acted as the first trigger, but rapid remission of nodules after specific antibiotherapy suggests the infectious etiology.

The list of possible etiologic factors in EN is extensive and infectious agents should always be considered in the differential diagnosis.

In the currently available literature, there is little research on skin manifestations associated with Covid-19. Two more cases of erythema nodosum associated with Covid-19 were reported, both with favorable evolution. [10-11].

In a retrospective cohort study, EN relapsed in 26.6% of cases and was mostly attributed to infectious and drugs. Except for drug-induced EN, factors responsible for EN' first manifestation frequently differed from those causing relapses in the same patients.[17]

Figure 4. Erythema nodosum lesions at 7 months after onset.

In the pediatric population, among the most frequent etiologic factors for EN are gastrointestinal infections with Salmonella enteritidis and Yersinia enterocolitica [18-20].

Conclusions

The Covid-19 infection might be the first trigger of EN, subsequently maintained by gastrointestinal and pharyngeal infectious agents.

This paper is the first Romanian publication presenting an association between Covid-19 infection and relapsing EN, in a young patient without other diseases.

It is extremely difficult to prove that there is a true link between infectious disease and EN. Usually, viral or bacterial infections are assumed to be a causal factor when they occur a few days before EN onset, and when other classical causes of EN can be ruled out.

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Conflict of interest
NONE DECLARED

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