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Erythema nodosum – one symptom, many causes?

Rumień guzowaty – jeden objaw, wiele przyczyn?

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Abstract

Erythema nodosum is a skin lesion most often located on the anterior surface of the lower extremities. It initially appears as rounded nodules with a vivid red or purplish colour. Erythema nodosum may often be a predictive sign of systemic infectious or autoimmune diseases. Group A streptococcal infections, virological infections (cytomegalovirus and Epstein–Barr virus) and sarcoidosis are the most common aetiological factors of erythema nodosum. Certain drugs also may be the cause, whereas erythema nodosum is often idiopathic in clinical practice. It is more common in women. Erythema nodosum rarely affects children, but with equal prevalence in both sexes. It is important to note that basic diagnostic process should be performed in all cases of erythema nodosum. The diagnosis involves laboratory tests (complete blood count with differential, C-reactive protein levels, presence of rheumatoid factor, hepatic enzyme level) and medical imaging (chest radiograph, abdominal and thyroid ultrasound). Depending on the suspected etiological factor, the diagnostic process should be extended to include other, additional laboratory investigations. Erythema nodosum is caused by type IV delayed hypersensitivity reaction to a wide variety of possible stimuli. Additionally, circulating immune complexes cause complement activation in patients with erythema nodosum. The histopathological picture of skin lesions shows septal panniculitis (inflammation of subcutaneous fat tissue) with associated Miescher's radial granulomas – aggregates of small histiocytes arranged around a central cleft. The most important therapeutic approach in erythema nodosum is the treatment of underlying disorders, if identified. If this is not possible, less potent topical corticosteroids and heparinoid ointments are used.

Keywords: erythema nodosum, skin lesions, sarcoidosis, medications, bacterial infections

Streszczenie

Rumień guzowaty jest zmianą skórną występującą głównie na przedniej powierzchni podudzi w postaci małych guzków o barwie początkowo czerwonofioletowej. Jego pojawienie się jest często objawem predykcyjnym w kierunku rozpoznania wielu różnych chorób, najczęściej o podłożu infekcyjnym lub autoimmunologicznym. Do najczęstszych przyczyn występowania rumienia guzowatego należą infekcja paciorkowcowa typu A, infekcje wirusowe (cytomegalowirus i wirus Epsteina–Barr) oraz sarkoidoza. Wystąpienie rumienia guzowatego niejednokrotnie wiąże się także z przyjmowaniem różnych leków. Jednak w praktyce klinicznej występowanie rumienia guzowatego o nieustalonej etiologii nie należy do rzadkości. Zmiana ta zdecydowanie częściej występuje u kobiet. U dzieci pojawia się z równą częstością u obu płci, lecz znacznie rzadziej niż u dorosłych. W przypadku pojawienia się rumienia guzowatego obowiązkowo należy przeprowadzić podstawową diagnostykę, obejmującą badania laboratoryjne (morfologia z rozmazem ręcznym, pomiar stężenia białka ostrej fazy, czynnika reumatoidalnego, stężenia enzymów wątrobowych) oraz obrazowe (radiologiczne klatki piersiowej, ultrasonograficzne jamy brzusznej oraz gruczołu tarczowego). W zależności od podejrzewanego czynnika etiologicznego diagnostykę należy poszerzyć o badania dodatkowe. Rumień guzowaty powstaje w wyniku reakcji nadwrażliwości typu IV wg Coombsa, tj. komórkowej odpowiedzi na szeroki wachlarz antygenów. Dochodzi także do aktywacji układu dopełniacza przez krążące we krwi kompleksy immunologiczne. Badanie histopatologiczne zmian skórnych charakteryzuje się odczynem zapalnym przegród łącznotkankowych zrazików tłuszczowych w tkance podskórnej z występowaniem w ich centralnej części skupisk histiocytów, tzw. ziarniniaków Mieschera. W terapii najważniejsze jest leczenie choroby podstawowej. Jeżeli nie uda się znaleźć przyczyny pojawienia się rumienia guzowatego, stosuje się leczenie miejscowe przy użyciu glikokortykosteroidów o słabej sile działania oraz maści z heparynoidów.

Słowa kluczowe: rumień guzowaty, zmiany skórne, sarkoidoza, leki, infekcje bakteryjne

INTRODUCTION

Erythema nodosum (EN) is the most common clinical variant of panniculitis (inflammation of subcutaneous fat tissue). The lesion is associated with local inflammation caused by the necrosis of adipose tissue or its connective tissue septa[1]. Morphologically, EN appears as symmetrical nodules most often located on the anterior surface of the lower extremities. In clinical practice, their presence is often of predictive value for the diagnosis of many diseases. The aim of the paper is to discuss the pathogenesis, aetiology and the clinical course of EN.

HISTORY

The term "erythema nodosum," which defines a separate disease entity, was introduced in 1798 by a British dermatologist Willan[2]. At that time, the characteristics of the disease included a wide group of different erythematous lesions, which were more common in women. In 1860, the nature of EN was precisely defined and a concept of erythema multiforme was introduced by Hebra, with EN representing a separate group of cases. The description of cutaneous manifestations of EN proposed by Hebra has become the basis for subsequent generations of authors[3]. Since the beginning of the 19th century, knowledge on EN has become increasingly popular; however, its aetiology still remained ambiguous. Differences in scientific literature were associated with patient qualification, age and geographical region, in which a given research was conducted[4]. In the second half of the 19th century, rheumatic diseases were widely considered to be the main factor responsible for EN. Tuberculosis was considered to be the second leading cause, and it was found at the beginning of the 20th century that 90% of adult patients with EN were infected with *Mycobacterium tuberculosis*. Over the next few years, the range of possible causes has expanded significantly despite the fact that the aetiological factor cannot be identified in a large proportion of EN patients[5].

AETIOLOGY

The aetiology of EN is multifactorial. Furthermore, the list of diseases and/or causative factors is continuously growing. An extensive list of concomitant bacterial, viral, protozoal and fungal infections of the skin may be usually found in literature. The most important role is attributed to streptococcal infections (also in children) and those caused by cytomegalovirus and Epstein–Barr virus. Erythema nodosum may also develop in the course of pharmacotherapy, antibiotic therapy and oral hormone therapy in particular (Tab. 1)[6]. Autoimmune diseases, including connective tissue disorders, are relatively common causes of EN. The development of EN as a prodromal symptom of sarcoidosis is a classic example. Although EN is not a pathognomonic symptom of this disease, it is the most common skin lesion observed in its course. Erythema nodosum, along with systemic manifestations, arthritis and lymphadenopathy, is a component of the Löfgren syndrome in sarcoidosis. Patients with EN and confirmed sarcoidosis account for up to 25% of cases[7]. Erythema nodosum may also coexist with other systemic connective tissue diseases, such as systemic lupus erythematosus, antiphospholipid syndrome, and Wegener's granulomatosis[8]. Erythema nodosum affects 50% of patients with Behçet's disease[9].

Bacterial infections	• ***Streptococcus* spp. (mainly *Pneumococcus*) (CH)** • ***Yersinia* spp.** • ***Mycoplasma* spp.** • ***Chlamydia pneumoniae*** • ***Mycobacterium tuberculosis*** • ***Mycobacterium leprae*** • ***Neisseria gonorrhoeae*** • ***Salmonella*** • ***Shigella*** • ***Campylobacter*** • ***Bartonella* (CH)** • ***Borrelia burgdorferi***
Viral infections	• **EBV (CH)** • **CMV (CH)** • VHB and VHC • HSV • B19 • Varicella zoster virus (VZV) (CH) • Mumps virus (CH) • HIV
Parasitic infections	• *Ascaris lumbricoides* • *Blastocystis hominis* • *Entamoeba histolytica* • *Giardia lamblia* • *Toxoplasma gondii* • *Trichomonas vaginalis* • *Taenia solium, saginata*
Fungal infections	• *Aspergillus* spp. • *Candida albicans* • *Histoplasma capsulatum*
Systemic connective tissue diseases	• Systemic lupus erythematosus • Polymyositis, dermatomyositis • Systemic scleroderma • Vasculitis • Reiter's syndrome
Inflammatory bowel diseases	• Crohn's disease (CH) • Ulcerative colitis (CH)
Cancer	• Lymphomas • Leukaemias
Physiological states	• **Pregnancy** • Chronic stress, improper diet (reduced immunity)
Drugs	• **Antibiotics** (amoxicillin, ciprofloxacin, levofloxacin) • **Co-trimoxazole** • **Nonsteroidal anti-inflammatory drugs** (acetylsalicylic acid, diclofenac, naproxen) • Paracetamol, metamizole • Oral contraceptives • Proton pump inhibitors • Barbiturates • Sulfasalazine, azathioprine • Codeine • Carbamazepine • Lidocaine
CH – common in children.	

Tab. 1. The most important causes of EN[11–17]

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It should be also noted that there has been an increase in the incidence of inflammatory bowel diseases with EN affecting 10% of patients, especially in the paediatric and young adult population[10]. Furthermore, increased severity of skin lesions is closely correlated with the clinical activity of ulcerative colitis[8]. Erythema nodosum may also develop as a component of paraneoplastic syndrome. The most common cancers in which EN develops include haematopoietic tumours, i.e. leukaemias and lymphomas[7,11,12]. Sweet's syndrome (also known as acute neutrophilic dermatosis), which belongs to rheumatic diseases with the symptoms of pyrietic infection of the upper respiratory tract (most often of the palatine tonsils), and which occurs 1–2 weeks before the onset of EN-like skin lesions, is an interesting disease. The syndrome may precede acute myeloid leukaemia or multiple myeloma[13].

Erythema nodosum also develops in healthy individuals. The disease may affect healthy pregnant women, mainly in the first trimester (*erythema nodosum gravidarum*). In such cases, EN is clinically manifested by the same morphology and course as in non-pregnant patients, and is not a result of exposure to medications or infections. Such lesions may or may not occur in subsequent pregnancies. Erythema nodosum in pregnancy may be due to increased oestrogen production or, more likely, altered oestrogen/progesterone ratio. The role of hormonal aetiological factors in the development of EN is supported by higher EN rates in women vs. men[14]. It should be also mentioned that contemporary oral hormonal agents belong to the most common pharmaceuticals inducing EN.

PREVALENCE

Erythema nodosum is more common among women than men (more than 6-fold more common during the 2–4 decades of life). The disease is extremely rare in the elderly (over 65 years of age)[15]. In the British population, the incidence is 2–3 cases per 100,000 inhabitants per year[1]. Also, a seasonal pattern of the incidence, with more cases reported in the spring and autumn, was observed, which may be associated with an increased frequency of infections caused by *Streptococcus* spp. at that time[16]. Erythema nodosum rarely affects children, and with equal prevalence in both sexes.

DIAGNOSIS

In the case of a patient diagnosed with EN, detailed medical history, including family history, comorbidities and pharmacotherapy used (including emergency use of drugs, such as over-the-counter drug, OTSs), is always needed. This should be followed by basic laboratory and imaging tests as well as additional tests, depending on the suspected aetiological factor (Fig. 1)[11,17]. Increased erythrocyte sedimentation rate (ESR) (above 50 mm/h) and C-reactive protein (CRP) levels are observed in most patients with EN. Minor leucocytosis with the domination of neutrophils develops. Also, increased serum aminotransferase activity and elevated α-2-globulin may be observed in some cases. The rheumatoid factor usually remains negative[1]. High antistreptolysin O titer is observed in cases of EN preceded by streptococcal upper respiratory infection. Chest radiography is needed in each patient diagnosed with EN as enlarged lymph nodes in the pulmonary hila or lung parenchymal lesions typical for sarcoidosis are present in about 50% of cases[1]. Tuberculin sensitivity test is also recommended to exclude infection with *Mycobacterium tuberculosis*[7]. In the case of uncertain EN aetiology, serological tests to detect less common bacteria, viruses, fungi or protozoa are recommended. A deep biopsy of the nodules with a specific histopathological picture is a confirming, though non-routine test (only in cases of unclear clinical picture)[1,9].

However, despite the use of all detailed additional tests, the aetiology of EN remains unclear in many cases[8]. According to some sources, more than half of EN cases are idiopathic (55%)[10,18,19].

PATHOGENESIS

Erythema nodosum develops as a result of non-specific type IV hypersensitivity reaction according to Coombs. This is a cellular response to a wide array of pathogens[11]. Skin lesions are most likely the result of immune complex

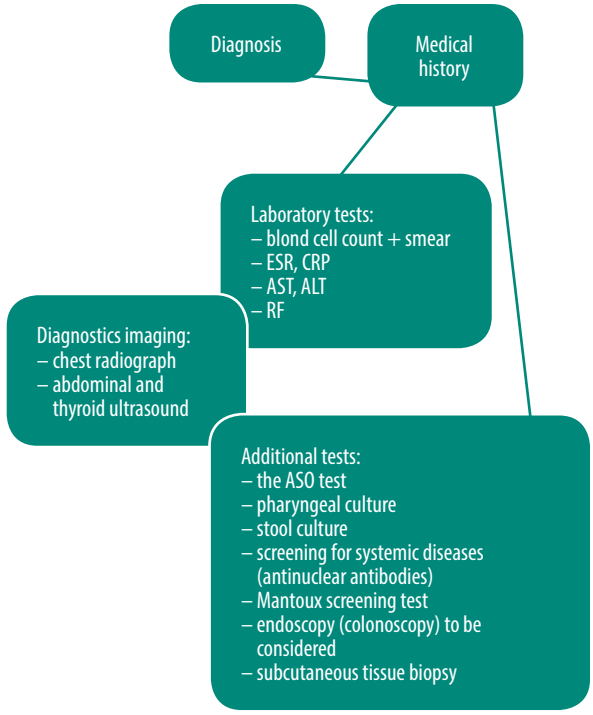

Fig. 1. Diagnostic management to determine the aetiology of EN (author's analysis)

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deposition in both the skin vessels and the septa between fat lobules[8]. Furthermore, the complement in the blood is activated by the circulating immune complexes. The disease is never accompanied by vasculitis, which is of importance for differential diagnosis. Immunofluorescence of the skin biopsy from fully developed lesions confirms late-onset reaction[11]. Increased production of reactive oxygen species (ROS) by activated neutrophils, whose serum levels correlate with the severity of EN, was observed in patients with EN. This indicates an important role of ROS in the pathogenesis of EN[8].

Histopathology of skin lesions reveals inflammatory reaction of connective tissue septa that divide the subcutaneous adipose tissue lobules. As a consequence, infiltration, which is initially composed of neutrophils, followed by lymphocytes and eosinophils, occurs in this region. This causes oedema and inflammatory infiltration of the subcutaneous tissue and around the veins[8,10]. Well-delineated clusters of histiocytes in the central part of skin lesions, the so-called Miescher's radial granulomas, are a typical finding in EN[20]. Fibrosis at the site of granulation tissue occurs; however, formation of scars, necrotic lesions or fistula is never observed[1,11].

The reason for the characteristic location of EN skin lesions, which are usually limited to the extensor aspects of the lower legs, is interesting, but unfortunately not fully understood. The location on the lower extremities is most likely due to anatomical conditions, i.e. relatively poor arterial and venous supply and a significant gravitational load of this body region. Additionally, the skin lacks an appropriate muscle pump, and the lymphatic system is not sufficiently developed in this region. Perhaps the tissues located in this area have a limited potential to respond to potentially irritating factors[17].

CLINICAL MANIFESTATIONS

Local manifestations

The clinical course of EN is quite characteristic. It manifests by the sudden onset of symmetrical, initially tender and warm nodules varying from 1 to 20 cm in diameter. The lesions are located symmetrically on the anterior aspects of lower legs (below the knee), and rarely involve the subcutaneous tissue of the arms, trunk, neck or face[8]. They are not clearly separated from healthy tissues. Colour evolution is quite characteristic of EN. At first, the nodules are raised slightly above the skin and show a bright red colour. Within a few days, they become flat, with a brownish-green colour. In the final period of the disease, they exhibit a yellow appearance. The lesions resolve gradually, within 2–6 weeks[17,21], leaving no scars, necrosis or malacia[11]. Erythema nodosum is characterised by a much shorter duration and lower relapse rates in children[8]. Mild postinflammatory hypo- or hyperpigmentation may be observed in this age group[22].

General symptoms

The development of nodules is most often accompanied by prodromal, systemic symptoms such as a subfebrile or feverish state, malaise, fatigue, joint pain, headache or abdominal pain. Nausea, vomiting and diarrhoea may also occur. Depending on the causative factor, conjunctival symptoms may also develop. Lymphadenopathy and/or hepatosplenomegaly may be observed in viral infections[7]. These symptoms may or may not occur about 3 weeks before skin lesions. Patient's medical history often reveals recent upper respiratory or gastrointestinal infection. In 90% of cases, skin lesions are preceded by inflammatory lesions accompanied by oedema and pain within the ankles[11]. Arthritis usually resolves simultaneously with skin lesions, with longer persistence in only few cases.

TREATMENT

If EN develops as a manifestation of another disease, the management of the underlying disease should be a priority. The treatment is conservative; rest with elevation of lower limbs is recommended. Nonsteroidal anti-inflammatory agents are used to provide pain relief. Less potent glucocorticosteroids (hydrocortisone, dexamethasone, flumethasone) as well as ichthyol and heparinoid-containing ointments are used topically. Although systemic glucocorticosteroids are not recommended due to possible infectious aetiology, their use may be needed in patients with lesions persisting longer than 6 weeks[1]. However, identification of the cause of EN and the treatment of the underlying disease are a priority.

CONCLUSIONS

Although EN is rarely encountered in clinical practice, it is a symptom that may suggest multiple aetiologies. Therefore, EN poses a challenge for general practitioners as accurate diagnosis largely depends on the initial diagnostic management.

Conflict of interest

The authors do not report any financial or personal connections with other persons or organizations, which might negatively affect the contents of this publication and/or claim authorship rights to this publication.

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