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ERYTHEMA NODOSUM IN THE COURSE OF MYCOPLASMA PNEUMONIAE INFECTION AND PREGNANCY IN A 17 – YEAR-OLD PATIENT

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ABSTRACT

Erythema nodosum is the most common form of panniculitis in the paediatric population. It is manifested by painful tumours in shades of red within the subcutaneous tissue, most often within the lower legs. Mild, non-specific systemic symptoms may occur. The course of erythema nodosum is associated primarily with local pain, sometimes implying motor disorders. Erythema nodosum may be primary or secondary as a manifestation of a systemic disease, medication or pregnancy. Although the course is often self-limiting, detecting erythema nodosum requires a systematised diagnosis of potential causative diseases. A detailed medical history and physical examination are vital in this process. Treatment of erythema nodosum most often consists of administering analgesics and anti-inflammatory drugs. Proper causal treatment of the primary disease is more important. The paper presents a case of a teenage girl with an intense course of erythema nodosum, in whom two probable causes of its occurrence were found.

KEYWORDS: Erythema nodosum, Mycoplasma pneumoniae, pregnancy

Erythema Nodosum (EN) is the most common inflammation of the subcutaneous tissue (panniculitis) in children. The inflammatory process involves connective tissue septa separating the adipose tissue lobules without accompanying vasculitis [1]; EN may be idiopathic or associated with a wide variety of systemic diseases, infectious and non-infectious, drugs, autoimmune diseases, and malignancies; it is suggested that pregnancy may also be an etiological factor this disease. Clinically, EN is characterised by symmetrical, painful, red or purple subcutaneous nodules, usually located on the front surface of the shin, with a diameter of 1-5 cm

[2], sometimes these lesions occur in less typical locations (upper limbs, thighs, buttocks, trunk, face). Although the coexistence of vasculitis has not been confirmed in the course of this disease, the vasculitis occurring in their vicinity may cause local transudate and thus increase the oedema of the subcutaneous tissue [2]. The skin manifestation is often preceded by non-specific prodromal symptoms such as low-grade fever, malaise, weight loss, joint pain, and symptoms of catarrh of the digestive tract and upper respiratory tract [1,2]. In the period of 2-8 weeks, a gradual regression of inflammatory changes is observed, preceded by a decrease in the cohesiveness of the nodules and a change in their colour to greenish or yellow (resembling bruises). Destructive in the skeletal system [1].

This condition most often occurs between the 2nd and 4th decades of life. In the age group up to 12 years of age, EN is equally typical in boys and girls and from puberty more often in females [2,3,4]. The aetiology varies depending on the population, geographical area or seasonality. More frequent occurrence of EN in the winter and spring period has been proven. According to the literature, approximately 30-70% of cases are idiopathic [1,2,5]. There are few reports on this disease in children in the scientific literature. This article aims to familiarise paediatricians with the clinical picture, diagnosis and treatment of EN.

CASE REPORT

In April 2020, to the Night Clinic and Christmas Medical Aid for Children in Bytom, a 17-year-old female patient reported poorly demarcated, red, warm nodular lesions in the subcutaneous tissue on the extensor side of both lower limbs. There was also swelling of the large joints of the lower extremities. Medical advice was held via ICT systems related to the COVID-19 pandemic two days earlier. The patient was diagnosed with urticaria, and topical therapy (fluticasone propionate ointment) was prescribed. In the history, infectious diseases were excluded for two months before the onset of inflammatory skin lesions. In February 2020, diagnosed with HPV infection, cryotherapy of genital warts was used therapeutically. Recently, the patient has not used any oral medications, including hormonal contraception. She confirmed regular sexual contact with the use of barrier contraception by her partner. For several years, she had been regularly consulted by a nephrologist due to polycystic kidney disease and remained under the neurologist's supervision due to a history of syncope. The physical examination revealed symmetrical, nodular, red lesions on the lower legs, up to several centimetres in diameter, slightly elevated above the skin level. A multitude of lesions and swelling of the ankle joints distorted the contours of this part of the limbs. The patient reported local pain in the lower legs, which intensified while walking. Apart from the described skin lesions, caries and scars after scratches on the skin, no other abnormalities were found on physical examination. Based on the typical clinical picture, the patient was diagnosed with erythema nodosum.

Since this type of cellulitis is often a manifestation of another disease process in the body, the patient was referred for treatment and diagnostics to the Paediatric Clinic of Specialist Hospital No. 2 in Bytom.

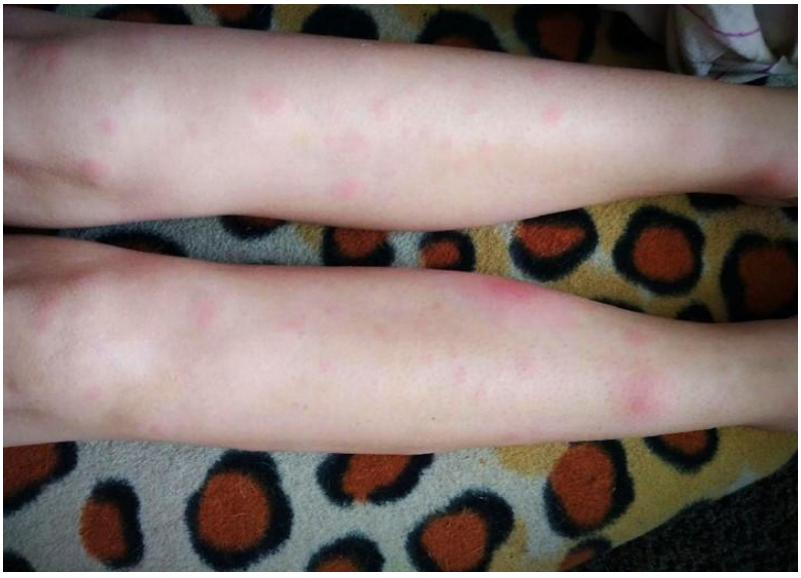

Fig. 1. Image of skin changes on the day of admission.

Stage one (carried out in conditions of holiday duty).

Diagnostic test results: slight leukocytosis with a predominance of neutrophils, elevated C-reactive protein (CRP) concentration 41 mg/l (N < 5 mg/l), accelerated ESR 65 mm/h (N<12 mm/h), slightly elevated antistreptolysin

(ASO) titre 225 IU/ml (N<200 IU/ml). Bacteriological tests (throat swab, stool culture) were negative. Immunological diagnostics were planned to exclude infectious agents as the cause of EN, including the diagnosis of Mycoplasma pneumoniae infection. Abdominal ultrasonography was performed and confirmed the presence of single cysts in both kidneys.

Treatment:

On the first day, empirical antibiotic therapy was administered: intravenous amoxicillin + clavulanic acid (3.6 g/day), topical NSAIDs (phenylbutazone) twice a day and oral diclofenac (100 mg/day), oral omeprazole (20 mg/day). After several days of treatment, the skin lesions persisted. The nodules were darker and more prominent. In addition, new eruptions appeared on the lower legs and single ones on the forearms.

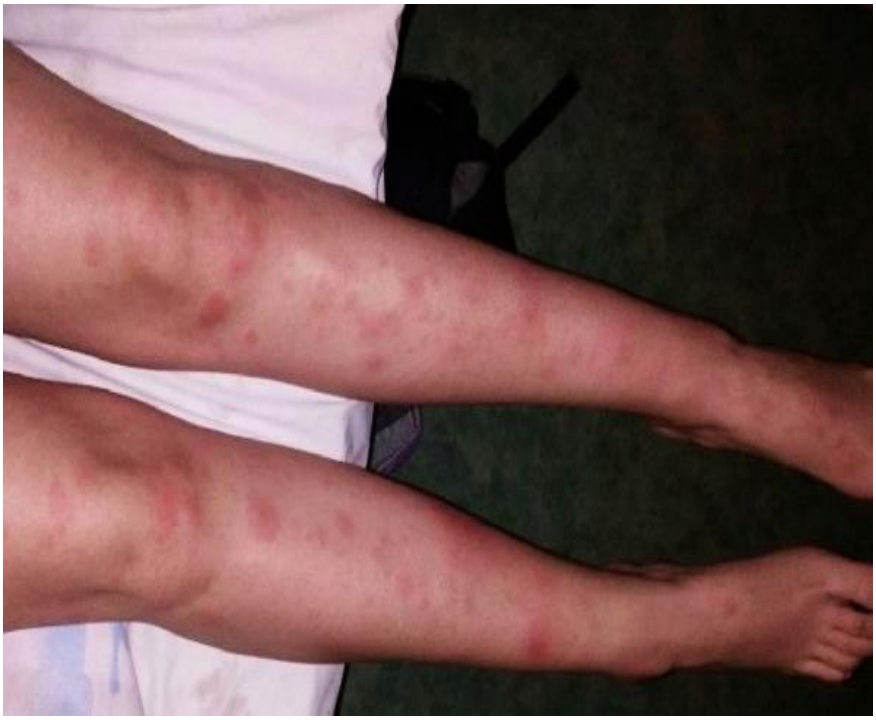

Fig. 2. Image of skin changes on the 6th day of the disease.

Stage two

A control laboratory test after three days showed a further increase in inflammatory parameters: CRP 67 mg/l, ESR 82 mm/h, and anaemia. On the fourth day of hospitalisation, the result of the antibody titre towards Mycoplasma pneumoniae was obtained, which showed an elevated concentration of IgM antibodies (15.0 AU/ml; N< 10 AU/ml). Due to the uncertain gynaecological history, the concentration of beta-HCG was determined, which was elevated (1145 IU/l). The consulting gynaecologist revealed a gestational sac (GS) in an ultrasound examination. The planned chest X-ray examination was abandoned.

Treatment:

After receiving a positive result for Mycoplasma pneumoniae infection and a diagnosis of infection with atypical bacteria, a macrolide was started. FDA class B erythromycin (at a dose of 1g/day) was used, reducing the pain of nodules with no new eruption. Due to abdominal pain and nausea reported after a few days of therapy, a decision was made to discontinue erythromycin and use azithromycin (500mg/day), which is approved for use in pregnancy.

Final diagnosis: Erythema nodosum during Mycoplasma pneumoniae infection and pregnancy.

Due to the resolution of skin lesions and normalisation of inflammatory parameters on the 8th day of hospitalisation, the patient was discharged home with a recommendation for further gynaecological care.

Stage three (relapse)

Three days later, the patient returned to the Emergency Room of the Pediatrics Clinical Department due to the recurrence of her symptoms. The general condition was average, suffering, and gait uncertain. In addition, she reported pain in the lower abdomen of a stabbing nature. Physical examination revealed massive swelling of the feet, ankles, knees, and fingers. On the lower and upper extremities, the typical erythema nodosum and hard nodular eruptions reappeared in a range of pink to purple colours. After consultation with the Department of

Rheumatology at the Paediatrics Center in Sosnowiec, the patient was urgently referred for further diagnostics and treatment at the hospital.

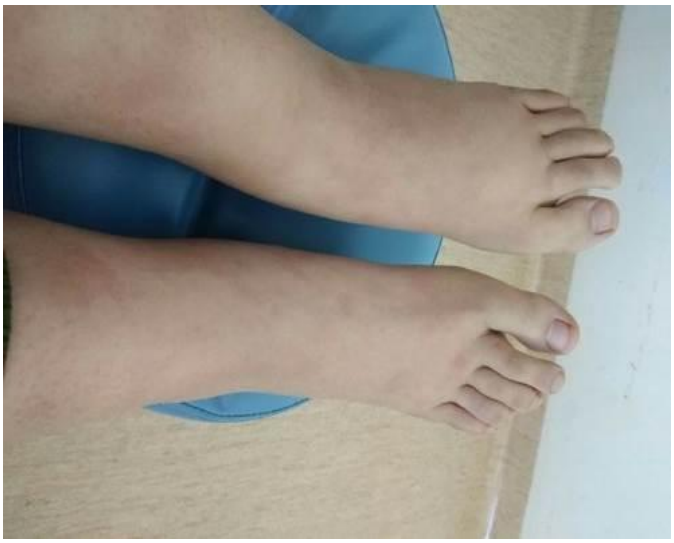

Fig. 3. Image of the lower legs at the second attack of the disease.

Stage four (hospitalisation at the Rheumatology Department)
Laboratory tests in the blood showed: high levels of inflammatory parameters: CRP 177 mg/l, ESR up to 106 mm/h, ferritin 697 ng/ml (N 5-148 ng/ml), decreased albumin concentration 28.7 g/l (N 40.2-47.6 g/l) with an increase in the percentage of alpha-1 and alpha-2 globulins. Extensive diagnostics were performed for infectious and systemic diseases. Mycoplasma pneumoniae IgM antibody titer was borderline (10 UA/ml, N<10 UA/ml) with negative IgG (7.66 UA/ml, N <10 UA/ml). The following were excluded: tuberculosis infection (QuantiFERON-TB negative) and spirochete pallidum (VDRL test negative). HIV, HCV, Chlamydophila pneumoniae and borreliosis were excluded based on negative antibody concentrations. The history of EBV and CMV infections was confirmed, but the avidity of IgG antibodies was high. An inflammatory process within the intestines was excluded (standard ultrasound image of the abdominal cavity, low concentration of calprotectin in the stool, negative ASCA). The presence of markers of vasculitis (negative pANCA and cANCA) was excluded. No antibodies suggestive of chronic connective tissue disease were detected in the ANA2 and ANA 3 panels (RNP/Sm borderline, negative: Sm, SS-A native, Ro-52 recombinant, SS-B, Scl -70, PM-Scl, Jo-1, Centromere B, PCN, dsDNA, Nucleosomes, Histones, RIB, AMA-M2, DFS 70). The ultrasound image of the musculoskeletal system showed a slight effusion in the knee joints, tendon sheaths of the peroneal muscles and inflammation of the subcutaneous tissue of the lower legs and fingers 2-5 of the hand. The consulting gynaecologist associated lower abdominal pain with adaptive uterine enlargement. After performing the diagnostics, the doctors from the Department of Rheumatology confirmed the earlier diagnosis. At the same time, they did not show an additional triggering factor for erythema nodosum. Due to the recurrence of symptoms in a short time and the severity of the symptoms, oral prednisolone at a low dose (15 mg/day) was included in the treatment, which was gradually reduced with good effect. After less than three weeks, all symptoms disappeared. In December 2020, the patient gave birth to a healthy baby.

DISCUSSION

In Poland, EN's most common infectious cause (accounting for up to 1/3 of cases) is infection with group A β-haemolytic streptococci [5]. Streptococcal pharyngitis usually precedes the onset of erythema nodosum by 2-3 weeks [2]. Several studies (Kakourou et al., Greco et al., Shimuzu et al., Aydin-Teke et al.) showed that one of the most common infectious agents associated with the development of EN was Mycoplasma pneumoniae infection, with some patients not presenting respiratory system involvement [6,7,8,9]. Skin manifestations occur in 10-25% of all Mycoplasma pneumoniae infections, including urticaria, vasculitis, Stevensen-Johnson syndrome, epidermal necrolysis, pityriasis rosea and the erythema mentioned above nodosum [8].
In the adult population, the second cause of the development of erythema nodosum is sarcoidosis, especially among young women, but it is rare in children [1,5]. Other causes of erythema nodosum include autoimmune diseases and cancer [1,2,5]. It is worth noting that EN occurs in 3-15% of patients with inflammatory bowel disease, which correlates with exacerbation of this disease [7]. The symptom also affects about 4% of pregnant

women. It usually takes place in the first or second trimester, but a case of a woman in the postpartum period has also been described [10,11]. The pathogenesis of EN has not been fully understood. Still, it is suspected that it may be related to immunological mechanisms in conjunction with hormonal changes (changes in the ratio of estrogen to progesterone) [10]. The diagnosis of EN is based on the clinical picture. When making the diagnosis, many secondary causes of erythema nodosum should be excluded, which is why the history taking into account infectious and chronic diseases, medications, and travel is essential [8]. There are no specific laboratory tests to help diagnose EN. Therefore, it is recommended to perform a wide range of additional tests to exclude infectious agents and systemic diseases. These tests should be carried out considering the existing indications [1,2,5]. Skin biopsy is not usually necessary but should be considered an atypical disease. If a subcutaneous tissue biopsy is needed, it is recommended to make a deep incision to collect the material for examination [1,2,5,10] properly.

The differential diagnosis should include infectious dermatitis or cellulitis, Schonlein-Henoch purpura, battered baby syndrome, urticaria, erythema sclerosis, fatty tissue necrosis, cutaneous nodular arteritis, insect bites, erysipelas, α1-antitrypsin deficiency[1, 5.10].

Primary = Idiopathic EN
Secondary EN • infections o bacterial: group A ß-hemolytic streptococci, Mycoplasma pneumoniae, endemic Mycobacterium tuberculosis, Yersinia entercolitica, Yersinia pseudotuberculosis, Campylobacter jejuni, Salmonella enteritidis, Chlamydia trachomatis, Bartonella henselae o viral: EBV, HBV, HCV, CMV, parvovirus B19, HIV, SARS-COV-2, HSV, VZV o fungal o protozoan: *Giardia lamblia, Entamoeba histolytica, Toxoplasma gonidii* • systemic diseases o sarcoidosis o inflammatory bowel disease o Behçet's disease o celiac disease o autoimmune hepatitis o spondyloarthritis o vasculitis o illness • cancers o lymphoproliferative o solid tumours (carcinoid, sarcoma) • medicines o antibiotics, PPIs, everolimus, aspirin, oral contraceptives, phenytoin, valproic acid, o vaccinations: BCG, DTaP, HPV, SARS-CoV-2 • pregnancy

Tab. 1 Aetiology of erythema nodosum

Most cases of erythema nodosum resolve spontaneously. Symptomatic treatment is mainly used (including analgesics and heparin ointments), and rest is recommended in bed with raised lower limbs to reduce discomfort [1,10,11]. As soon as the etiological factor of erythema is detected, it is essential to treat the cause (antibiotic therapy, antifungal, antimycobacterial, antiparasitic drugs, and treatment for exacerbation of chronic systemic disease) [2,5].

In idiopathic erythema nodosum, NSAIDs are used, and in resistant cases, systemic steroid therapy and anti-TNF antibodies [2,5,10,11].

The case described in the paper is valuable in terms of training due to its characteristic manifestation (typical nodular changes on the skin, swelling of the subcutaneous tissue, joint pain, malaise), compliance with epidemiological data (female sex, second decade of life, spring period) and the detection of two etiological

factors (Mycoplasma pneumoniae and pregnancy). Performing basic biochemical tests would not allow determining the cause of the disease (increased inflammatory parameters are not specific, especially since the increase in the concentration of CRP, the percentage of alpha-1 and alpha-2 globulins is typical for acute inflammatory processes, and is also possible during pregnancy [11]). During the stay in the Paediatrics Department, a broader diagnostics was focused primarily on infectious agents (stool culture, throat swab, ASO, anti-Mycoplasma antibodies), and in the conditions of the Rheumatology Department on contagious and systemic diseases (ANA 3, ANCA, ASCA, anti-CCP, RF, antiphospholipid antibodies, complement components, protein gram, VDRL, HIV, HCV, Quantiferon, EBV profile, p/CMV antibodies; high avidity of EBV IgG and CMV IgG allowed for the diagnosis of a former infection). The holiday season was not without significance for the efficiency of the diagnostic process. The case of a teenager shows that, regardless of the gynaecological history, in many cases, it is crucial to determine the concentration of β-HCG early because the possible diagnosis of pregnancy entails the need to modify the diagnostic (here X-ray) and therapeutic procedures (safety of drugs according to the FDA classification). We suspect that the high number of lesions in the first phase and the occurrence of the second phase of the disease may have resulted from the existence of two causative factors, perhaps acting at different times or synergistically. Ultimately, according to the literature, symptoms resolved in just over three weeks without complications. A side observation that occurred to the authors of the study, as well as to many doctors working in hospital wards, is the insufficient role of teleconsultations in the diagnostic and therapeutic process and limited access to the services of primary care physicians, especially in the era of the COVID-19 pandemic, was often associated with the wrong care process medical over the patient.

The authors of the work are employees of both the Clinical Department of Paediatrics in Bytom (currently headed by Dr Krystyna Stencel Gabriel, MD, and during the patient's stay by Prof. Anna Obuchowicz, MD) and the hospital's Night and Holiday Health Care Clinic. We want to thank the doctors from the Department of Paediatric Rheumatology in Sosnowiec (under the direction of Anna Gruenpeter, MD, PhD) for caring for the patient and providing the necessary medical data.

The study was conducted in accordance with the Declaration of Helsinki. Ethical review and approval were not required for case studies according to the national regulations.

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