SURGERY

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Power to dissolve the bone: Autoinflammation behind the curtain. An update on chronic recurrent multifocal osteomyelitis with clinical case presentation

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Multifaceted presentation of rheumatic diseases makes patients to consult physicians of various medical specialties, including surgeons. In this paper we present a case of pediatric patient with chronic recurrent multifocal osteomyelitis — an autoinflammatory bone disorder — who was misdiagnosed a lot and thus improperly treated before coming to the rheumatologist. An extensive review of scientific papers on chronic recurrent multifocal osteomyelitis was also conducted to show recent advances in the disease imaging and treatment. Our case illustrates that autoimmune and autoinflammatory disorders are not solely the matter of rheumatologist's concern. Physicians of different specialties, including surgeons, should be aware of miscellaneous clinical signs of rheumatic conditions to propel their prompt, accurate diagnosis and efficient treatment.

Keywords: autoinflammatory disorders, chronic recurrent multifocal osteomyelitis (CRMO), misdiagnosis, clinical case.

Introduction

Extensive research on immune system gives rise to determine immunity as a powerful guardian angel, somehow prone to become a renegade and destroy self when improperly taught or misguided by hostile invaders. Being ubiquitous, immunity has its representation throughout the body, and there's no organ system potent to escape from autoimmune

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disorder when it occurs. Multifaceted presentation of rheumatic diseases makes patients to consult physicians of various medical specialties, including surgeons. Frequent misdiagnosis at the first manifestation takes a lot of precious time to start an appropriate treatment, leads to unnecessary antibiotic prescription and even surgery. This is what our story about.

One can think autoimmune conditions are uncommon. However, according to the proceedings of Annual European Congress of Rheumatology (EULAR 2019), a third of people of all ages are somehow affected by a rheumatic disease during their lifetime. Although the topic of our discourse, chronic recurrent multifocal osteomyelitis (CRMO), is rare in individuals, as a whole it afflicts a large group of people. The key message today is one proposed by the International Rare Diseases Research Consortium (IRDiRC) in the goals for 2017–2027: "The time has come for researchers, clinicians, and patients worldwide to collectively understand the etiology of the vast number of rare diseases and make the final push to enable an efficient diagnosis for patient".

Here we **aim** to tell the story of pediatric patient with CRMO who was misdiagnosed a lot and thus improperly treated before coming to the rheumatologist. An extensive review of scientific papers on CRMO was also conducted to show recent advances in CRMO imaging and treatment.

Discussion

To begin with, rheumatic diseases can be divided into two groups: autoinflammatory and autoimmune disorders. Clinical presentation of both types of diseases overlap, but pathological pathways underlying rheumatic autoinflammation and autoimmunity are distinct. Whereas autoinflammatory diseases are mostly driven by inflammasome-induced IL-1β and IL-18 production, autoimmune diseases are associated with type I interferon (IFN) signatures in blood. Autoinflammatory disorders are characterized by seemingly unprovoked episodes of systemic inflammation in the absence of self-reactive T cells or high-titer autoantibodies [1].

Chronic recurrent multifocal osteomyelitis (CRMO) is an autoinflammatory bone disorder mostly affecting children and adolescents, characterized by aseptic inflammation in the metaphyseal parts of long bones, the pelvic bones, the vertebral column, or the shoulder girdle/clavicle, and less frequently — in the other parts of the skeleton [2].

CRMO becomes a real conundrum for a general practitioner since persistent joint pain, which still remains the main reason to consult a rheumatologist, is uncommon in these patients. Even for a specialist in the field, the diagnosis of CRMO can be complicated by clinical overlap with other autoimmune or autoinflammatory disorders and absence of specific disease biomarkers or gene signatures [3]. The only existing diagnostic criteria for CRMO (Jansson A. et al., remote 2007 [4]) remain helpful in the process of decision-making but often considered to be vague and still haven't been globally accepted (Table 1).

To avoid unwanted antibiotics prescription and surgical interventions, CRMO must be differentiated from many infectious, genetic, and oncological diseases. The choice of the best CRMO imaging and, especially, treatment option still remains highly disputable. Generally, medications with reported efficacy in CRMO refractory to NSAIDs include non-biological disease modifying anti-rheumatic drugs (DMARDs), inhibitors of tumor necrosis factor-α (TNFi), and bisphosphonates. However, even within Russia [5; 6] views of rheumatologists on these issues differ a lot.

Table 1. **Diagnostic criteria for CRMO proposed by Jansson et al., 2007 [4]**

Major criteria	Minor criteria
1. Radiologically proven osteolytic/-sclerotic bone lesion	1. Normal blood count and good general state of health
2. Multifocal bone lesions	2. CRP and ESR mildly-to-moderately elevated
3. Palmoplantar pustulosis or psoriasis	3. Observation time longer than 6 months
4. Sterile bone biopsy with signs of inflammation and/or fibrosis, sclerosis	4. Hyperostosis
CRMO is confirmed by two major criteria or one major and three minor criteria	5. Associated with other autoimmune diseases apart from palmoplantar pustulosis or psoriasis
	6. Grade I or II relatives with autoimmune or autoinflammatory disease, or with CRMO

Reductions: **CRP —** C-reactive protein; **ESR —** erythrocyte sedimentation rate

To shift the focus from general statistics to the history of single living human, we'll present a clinical case.

CLINICAL CASE
Patient A., female, born in 2001

On admission 13/03/2019: tenderness to palpation of the sternum, impaired mandibular movement and TMJ pain, gait abnormality due to heel pain, swelling and impaired movements in both ankle and left wrist joints.

History of present illness (please, see Fig. 1 for the detailed information)**:**

- to put the story into perspective, the disease manifested in patient A. in the age of fourteen with throbbing localized pain in the sternal manubrium and profound lymphadenitis, two weeks after acute tonsillitis. Obviously, at that time the condition was regarded as acute hematogenous osteomyelitis and treated with antibiotics, though no pathogen was seen in blood or biopsy sample;
- repeated antibiotic administration showed no effect, and extended biopsy with partial resection of the sternum was further performed. The surgery brought no significant relief in pain;
- several months later continuing osteomyelitis was suspected to be of autoinflammatory nature, concerning prior acute tonsillitis as a potential trigger of that condition. However, as NSAIDs prescribed had shown no effect, the diagnosis of CRMO was ruled out;
- then, the history of the misdiagnosis repeated itself: patient A. underwent surgery and antibiotic treatment again;
- at last, in November 2017, after having been consulted a professor in the Clinical Hospital for Children of Sechenov University, patient A. was finally diagnosed with CRMO and successfully treated with sulfasalazine (SSZ);

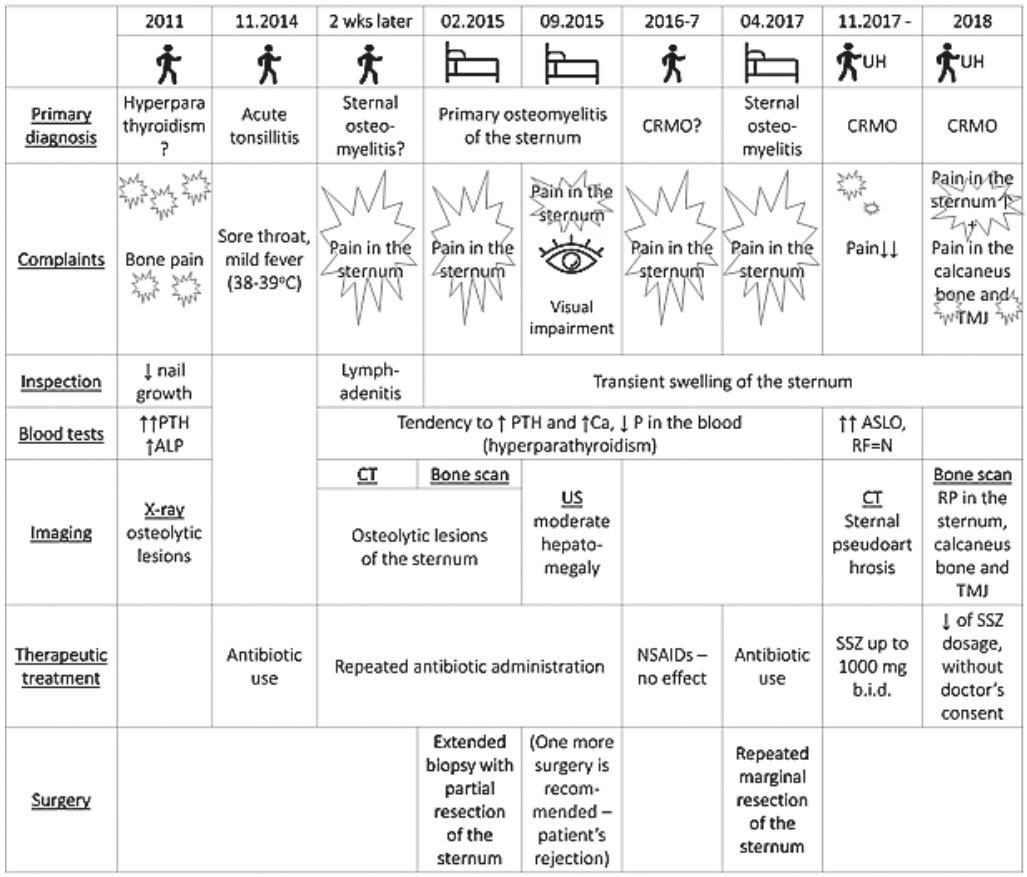

Fig. 1. History of the presenting complaints and past medical history of patient A

Abbreviations: **UH** — University Clinical Hospital for Children, Sechenov University; **CRMO** — chronic recurrent multifocal osteomyelitis; **TMJ** — temporomandibular joint; **PTH** — parathyroid hormone; **ALP** — alkaline phosphatase; **ASLO** — antistreptolysin O; **RF** — rheumatoid factor; **CT** — computed tomography; **Bone scan** = skeletal scintigraphy; **US** — ultrasonography; **NSAIDs** — nonsteroidal anti-inflammatory drugs; **SSZ** — sulfasalazine.

- then, within the improvement of overall well-being, patient A was seen to decrease SSZ dosage without doctor's consent, which triggered rebound of pain in the sternum with calcaneal and jaw bones involvement. Upon the return to the standard doses of SSZ, patient A. has sustained drug-induced remission.

Past medical history (see Fig. 1, 2): patient A. has multiple endocrinological disorders. Much attention should be paid to the hyperparathyroidism which could aggravate patient's condition: increased release of parathyroid hormone accelerates washing out of calcium from bones.

Family history (Fig. 2, 3): as seen from the family tree, patient A. tends to be genetically predisposed to metabolic (insulin resistance) syndrome. Remarkably, patient's father was previously diagnosed with rheumatoid arthritis, which presents as a one of the minor

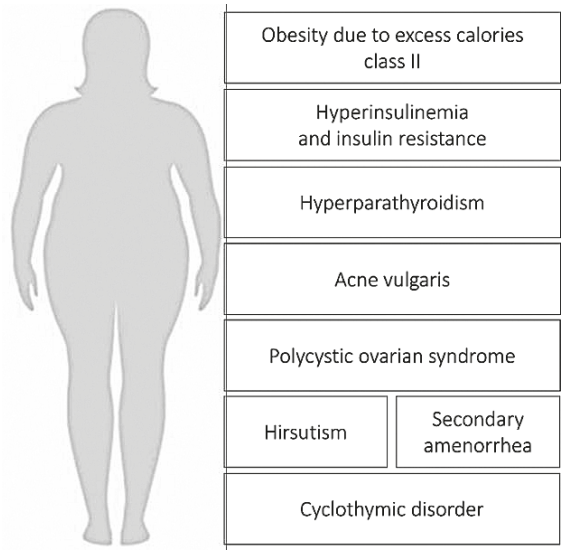

Fig. 2. Comorbidities observed in patient A.

diagnostic criteria for CRMO. Overall, patient A. was diagnosed according to 3 major and 3 minor criteria (Table 1).

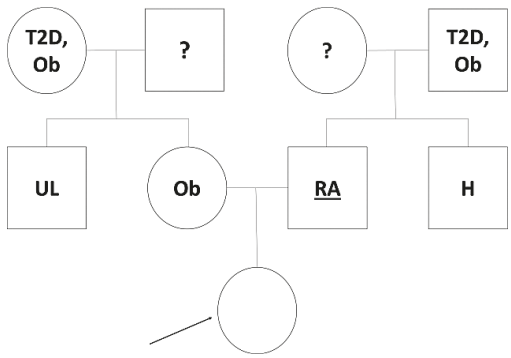

Fig. 3. Family history of patient A

Abbreviations: **T2D** — type 2 diabetes mellitus; **Ob** — obesity; **RA** — rheumatoid arthritis; **UL** — urolithiasis; **H** — healthy.

Having gone a long and thorny way to the proper diagnosis, patient A. has been further successfully treated with sulfasalazine (SSZ), without using any biologic drug.

Conclusion

Our story illustrates that autoimmune and autoinflammatory disorders are not solely the matter of rheumatologist's concern. Physicians of different specialties, including surgeons, should be aware of miscellaneous clinical signs of rheumatic conditions to propel their prompt, accurate diagnosis and efficient treatment.

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