Extensive Bone Infarctions - an Unexpected Consequence of Corticosteroid Treatment in Idiopatic Polymiositis

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The idiopathic inflammatory myopathies (IIM) are a group of autoimmune disorders characterized by chronic muscle weakness and the presence of inflammatory cell infiltrates in skeletal muscles. The current report presents a rare case of bone infarction in a patient with polymyositis, possibly related to the corticosteroid treatment, metabolic profile and long-term smoking history of the patient.

Keywords: polymyositis, bone infarction, corticosteroids

The idiopathic inflammatory myopathies (IIM) are a group of autoimmune disorders characterized by chronic muscle weakness and the presence of inflammatory cell infiltrates in skeletal muscles. They are further divided into polymyositis (PM), dermatomyositis (DM) and inclusion body myositis [1]. PM is a subacute myopathy associated with weakness in the proximal muscles of the upper and lower limbs and usually evolves in weeks or months. Diagnosing PM requires muscle biopsy due to multiple similarities shared with numerous other myopathies [2].

Corticosteroids such as prednisone with a starting dose of 1mg/kg/day or equivalents are the first line of therapy in PM. Steroid-sparing drugs such as azathioprine or methotrexate are also recommended in order to taper the corticosteroid dose, thus to prevent the risk of bone fractures and other side effects [3, 4].

Corticosteroids are potent anti-inflammatory drugs, synthetic analogues of the steroid hormones produced by the adrenal cortex, essential for the cessation of the inflammatory cascade as well as interference of the immune response in a variety of immune inflammatory pathologies. Glucocorticoids can be classified based on the chemical structure as follows: Group A – hydrocortisone type such as hydrocortisone, methylprednisolone, prednisolone and prednisone (short- to medium-acting glucocorticoids), Group B – acetonides such as budesonide, fluocinonide, halcinonide, Group C – Betamethasone type such as beclometasone, betamethasone, dexamethasone, Group D – Esters, Group D1 – halogenated such as alclometasone dipropionate, betamethasone dipropionate, Group D2 – Labile prodrug esters such as hydrocortisone aceponate, hydrocortisone acetate. Prednisone is the delta 1 derivate of cortisone and is converted in the liver by hydrogenation with the formation of a 11-hydroxy group in prednisolone, the biologically active form. It has a half-life in plasma of 60 minutes, the half-life of prednisolone being 200 minutes. Methylprednisolone is similar to prednisone. The side effects are comparable for both prednisone and methylprednisolone and most of them are dose and time-dependent. Notable are infections, osteoporosis, avascular necrosis, glucose intolerance, peptic ulcers, muscle weakness or hypertension.

Experimental part

We present the case of a 50-year-old female admitted to the Department of Neurology with a 4-month history of myalgias present in the muscles of the proximal segment of the inferior and superior limbs accompanied by muscle weakness. The patient had surgically-induced menopause one year before admission with a history of total hysterectomy with bilateral anexectomy for endometrial hyperplasia with atypia and is also known with primary arterial hypertension, type 2 diabetes in treatment with oral anti-diabetic drugs, dyslipidemia, non-alcoholic fatty liver disease, asymptomatic hyperuricemia and a gastric endoscopic polypectomy without any further reassessment. Also, the patient admitted she was a heavy smoker. The initial diagnosis was polyradiculoneuritis. However, the patient was transferred to the Department of Rheumatology for subsequent investigations and treatment due to the lack of any clinical or biological improvement, increased creatine phosphokinase (CPK) levels up to 9304 U/L and AST levels up to 220U/L. According to Targoff Criteria 1997, the patient was diagnosed with acute idiopathic PM and therefore was administered a total dose of 3g of IV methylprednisolone, followed by 64 mg per day of oral methylprednisolone due to prednisone intolerance, high dietary supplementation of calcium and vitamin D and then discharged after a significant improvement of myalgias, inflammatory syndrome and muscle enzymes. Two months later, after the patient presented with new-onset myalgias in the muscles of the proximal segment of the inferior limbs, marked arthralgias of the knee and ankle joints with limited motion range due to pain, accelerated intestinal transit,

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unintentional weight loss of approximately 5 kilograms in 2 months, fever and dysphonia.

The clinical examination revealed facial Cushingoid appearance, thrushes covered with white deposits in the oropharyngeal mucosa, edema extended to the proximal half of the calves, with mottled appearance of the skin – livedo reticularis, hypokinetic and hypotonic muscular system, pain caused by muscle compression in the proximal segment of the inferior limbs, pain during spine mobilization, positive Patrick's maneuver, limited mobility of both knees due to pain, pain in the right hypochondrium, the inferior margin of the liver at 6 cm below the right costal margin and mild pulsations of the peripheral arteries in the lower limbs.

The biological profile at admission showed a mild anemia with hemoglobin levels of 11.99 g/dL, hematocrit of 33.06%, leucocyte levels of 12,060/mm^3, intense inflammatory process with ESR levels of 80 mm/h, CRP 121.48 mg/dL and fibrinogen 725 mg/dL, CPK levels of 25.65 U/L, LDH 260.68 U/L, hypocalcemia with serum calcium levels of 7.80 mg/dL.

The immunological profile revealed elevated immunoglobulin G levels up to 408.81 mg/dL and positive anti-gp210 antibody on autoimmune disease panel, a very rare marker for PM.

The biopsy from the deltoid muscle revealed mononuclear inflammatory cells, predominantly CD8+ cytotoxic T cells, surrounding, invading and destroying healthy muscle tissue.

Regarding preliminary diagnosis, we ruled out an inflammatory etiology of the muscle pain given the primary disease and the lack of improvement in the patient's symptoms. Furthermore, we managed to exclude other pathologies such as septic arthritis, radiculoneuritis and paraneoplastic syndrome.

The musculoskeletal ultrasound (MUS) examination of the knees and ankles displayed a moderate hypoechoic collection in the suprapatellar and parapatellar recess of the right knee, marked subcutaneous edema located in the lateral compartment of the right knee, in the distal part of both calves, without any inflammatory changes in the ankles. 15 mL of yellow-green fluid were extracted and sent for cytology, bacteriology and culture examination. The examination of the synovial fluid revealed smears with hypercellularity represented by numerous polymorphonuclear leucocytes, frequent synovial cells distributed both isolated and in small groups, in normal cytology range, rare lymphocytes, rare erythrocytes and abundant cellular detritus, positive Rivalta reaction, negative acid-alcohol resistant bacillus (BAAR), glucose levels lower than 5 mg/dL, uric acid levels of 5.18 mg/dL, protein levels of 3.80 mg/dL. Cultures were negative for aerobe/anaerobe flora, fungal and mycobacterial infections.

The electromyography study revealed axonal primary motor polyneuropathy and also myopathic motor unit potentials, fibrillations, positive sharp waves and increased insertional irritability.

In order to exclude a possible malignancy, the patient underwent a thorax, abdominal and pelvic computed tomography (CT) examination which detected no significant changes.

The absence of improvement in the patient's clinical symptoms – intense pain in the lower limbs, focused mainly in the knee area and proximal tibia, persistent after repose, aggravated by walking, severe loss of articular function and intense edema of the subcutaneous cellular tissue around the knees, ankles and calves lead to further imaging investigations.

Initially, the patient underwent a unilateral right knee radiograph which revealed minimal degenerative changes in addition to cortical bone thickening and a heterogeneous serpiginous lesion with no visible signs of cortical bone disruption or extension in the adjacent soft tissues, located in the distal femoral metaphysodiaphyseal region. Furthermore, we followed the recommendation of the medical imaging team and sent the patient for a CT examination of the right knee which showed a similar aspect compared to the initial knee radiograph. However, the CT scanogram which is used to position the desired scanned area revealed a similar smaller lesion in the distal femoral metaphysodiaphyseal region of the left knee (fig.1).

Given the changes detected by the CT examination, we proceeded with a magnetic resonance imaging (MRI) scan of both knees. Coronal STIR 1.5 T MRI images revealed multiple heterogeneous iso- to hyperintense serpiginous lesions with surrounding peripheral hyperintense areas affecting both distal femoral metaphysodiaphyseal regions, left distal femoral epiphysis and both proximal tibial metaphysodiaphyseal regions. There were no visible signs of cortical bone disruption or extension in the adjacent soft tissues. The MRI aspect is highly suggestive for multiple bone infarctions (fig. 2).

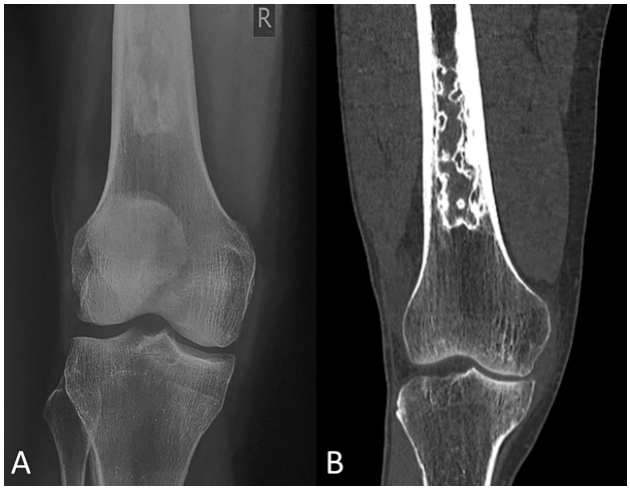

Fig. 1 (A, B). Minimal degenerative changes, cortical bone thickening and a heterogeneous serpiginous lesion with no visible signs of cortical bone disruption or extension in the adjacent soft tissues, located in the distal femoral metaphysodiaphyseal region (A). The CT examination of the right knee showed a similar aspect compared to the initial knee radiograph (B).

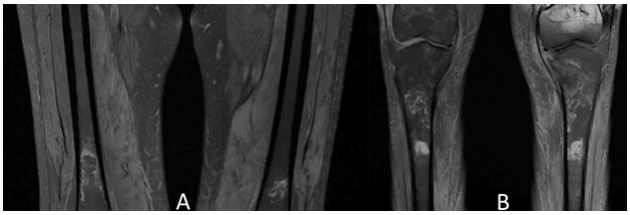

Fig. 2 (A, B). Coronal STIR 1.5 T MRI images revealed multiple heterogeneous iso- to hyperintense serpiginous lesions with surrounding peripheral hyperintense areas affecting both distal femoral metaphysodiaphyseal regions (A), left distal femoral epiphysis and both proximal tibial metaphysodiaphyseal regions (B). There were no visible signs of cortical bone disruption or extension in the adjacent soft tissues. The MRI aspect is highly suggestive for multiple bone infarctions

Given the clinical context, previous corticosteroid treatment and MRI structured report, our final diagnosis was multiple bone infarctions.

During hospitalization, the patient underwent treatment with azathioprine 100 mg per day, oral methylprednisolone

in tapering dose, non-steroidal anti-inflammatories, pain relievers, muscle relaxants, peripheral vasodilators and antibiotics with partial improvement of the symptoms.

Results and discussions

Following the PM diagnosis, the patient underwent treatment with high-dose methylprednisolone which lead to a partial remission of muscle pain. On the other hand, the patient also developed inflammatory knee pain and muscle weakness in the areas above and below the knee joints.

The most common side effects of corticosteroid treatment are related to structural bone changes such as osteoporosis, compression fractures and avascular necrosis [5]. Other side effects include Cushingoid appearance, cardiovascular involvement (such as hypertension), diabetes, cataracts and cortisone-induced myopathy [6]. The development of avascular necrosis depends on the duration of the treatment, the daily and cumulative corticosteroid doses [7]. Cortisone treatment determines the appearance of ischemia by stimulating the hypertrophy of fat cells leading to the reduction of blood flow and also by increasing the pressure inside the bone [8]. Avascular necrosis is used to describe changes in the epiphysis or subarticular bone after an ischemic injury, while bone infarction characterizes the metaphyso-diaphyseal bone lesions [9].

Bone infarction may have multiple causes such as trauma, sickle cell disease, Gaucher's anemia, Fabry's disease, infections, dyslipidemia, pancreatitis and diabetes. It may also be encountered in autoimmune and inflammatory disorders like systemic lupus erythematosus, rheumatoid arthritis, systemic scleroderma and gout. Other risk factors include the use of immunosuppressant drugs and corticosteroids, radiation therapy, alcohol abuse and smoking [10].

Hyperlipidemia may also be considered an inducer for avascular necrosis, mainly high levels of triglycerides and LDL and non-HDL cholesterol. A number of studies have proven that dyslipidemia associated with alcohol abuse or corticosteroid use increase fat deposition which may interrupt the blood flow to the bone. Also, obesity associated with elevated levels of plasma insulin concentrations can promote the appearance of bone infarctions. Heavy smoking leading to changes in nitric oxide bioavailability has also been incriminated as a risk factor [11].

These ischemic lesions occur mainly in the metaphysodiaphyseal segment of the long bones such as the femur and tibia and usually involve the lower limbs. They are frequently symmetrical and occur in multiple regions. Patients are usually asymptomatic, present mild symptoms or can mimic severe inflammation particularly in Gaucher's disease, sickle cell anemia or various types of malignant tumors [12].

Our patient presented several risk factors for bone infarctions. Initially, the patient underwent pulse corticosteroid therapy with methylprednisolone, followed by a short-term (less than two months) corticosteroid therapy with doses equivalent to 1 mg/kg/day and less than 100 mg prednisone, which may have contributed to an acute onset of this side effect. The patient's metabolic profile, including surgical-induce menopause and smoking history could have also accelerated the development of bone infarctions. Regarding differential diagnosis, several pathologies were considered. Septic embolism was excluded due to the absence of infection in the synovial fluid extracted from the knee joint. Also, we ruled out possible multiple metastatic bone lesions in the absence of a primary malignant tumor.

Conclusions

The current report presents a rare case of bone infarction in a patient with PM, possibly related to the corticosteroid treatment, metabolic profile and long-term smoking history of the patient, adding value to the current literature data which offers little information regarding the association of corticosteroid-induced ischemic bone lesions in patients with PM, although it occurs shortly after the initiation of therapy, less than two months, at recommended doses according to the treatment protocol.

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