dietary measures that favor oral hydration, the use of artificial saliva and, in the most severe cases, systemic therapy, for example, with cholinergic agents.[8,9]

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Case of familial mediterranean fever presenting with constant abdominal pain

Caso de fiebre mediterránea familiar con dolor abdominal constante

Dear Editor,

Familial Mediterranean fever (FMF) is a disease characterized by sporadic, serosal inflammation and unpredictable attacks of fever. This condition is thought to be hereditary and autosomal recessive. Patients often consult with fever, joint pain and intermittent abdominal pain, which progresses as an attack that does not last more than 3 days.[1] We discuss a case, rarely reported in the literature, in which the presenting symptom was continuous abdominal pain. An extensive study led to a diagnosis of FMF.

A 49-year-old man of Turkish origin came to our outpatient clinic with isolated, persistent abdominal pain. He had a 10-year history of abdominal pain in the form of continuous shooting pain in left upper quadrant. The attacks of abdominal pain were not very severe, but would last all day and, over the past 5 years, he had noted that the severity did not change upon eating or drinking. The patient had undergone examination with all the advanced radiological techniques, including exploratory laparoscopy focusing on possible sources of the abdominal pain, but no diagnosis had been reached.

The patient's vital signs on admission included a body temperature of 36.3 °C, pulse rate of 85 bpm, blood pressure of 140/90 mm Hg and respiratory rate of 13 breaths/min. There were no notable abdominal findings in the physical examination except tenderness on deep palpation in the left upper quadrant. Tests performed to determine the etiology included complete blood count, routine biochemistry, markers of hepatitis, urinalysis, stool microscopy and culture, thyroid function tests, anti-extractable nuclear antigen antibody profile, culture for *Salmonella* and *Brucella*, and tumor markers, and the results were normal or negative. Erythrocyte sedimentation rate was 25 mm/h (normal range, 0–20) and C-reactive protein level was 9 mg/L (0.2–5). In radiological examinations using advanced techniques, the findings in abdominal ultrasonography and computed tomography, esophagogastroscopy and colonoscopy were normal. Although the patient's clinical presentation was not suggestive of FMF, genetic testing was carried out with this disorder in mind. As a result, a homozygous R202Q mutation was detected. A Tru-cut biopsy taken from the rectum during the colonoscopy revealed AA amyloidosis. The patient was diagnosed with FMF on the basis of abdominal pain, the positive genetic test result and AA amyloidosis. The patient was started on colchicine 3 times daily. After 3 weeks of treatment, the patient's abdominal pain had completely resolved.

In FMF, patients often present with peritonitis, pleurisy, synovitis and skin lesions such as erysipelas. However, approximately 95% of the patients complain of localized abdominal pain. The pain, local at first, progresses to rigidity, adynamic ileus and rebound tenderness, and ultimately spreads to the whole abdomen. The attacks often last up to 3 days.[2] Familial Mediterranean fever is caused by a *MEFV* gene mutation,[3] which often occurs in exon 2 or 10. While the prevalent mutation (47–94%) is M694V in exon 10, previous genetic studies have shown that M680, E148Q, V726A, A744S, R202Q, R761H and T267 are also frequent mutations.[4] R202Q is a mutation that can be detected quite often in the Turkish population. In studies carried out in Turkey, it has been shown that heterozygous forms produce no symptoms and do not cause amyloidosis, but homozygous forms are associated with the development of symptoms and progression to amyloidosis.

Our patient was admitted to the hospital with a 10-year history of persistent isolated left upper quadrant pain. A homozygous R202Q mutation was detected in the genetic analysis and rectal biopsy revealed AA amyloidosis. The patient responded well to treatment with colchicine.

Thus, FMF should be considered in patients presenting with abdominal pain that is not characteristic of this disorder.

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Conflict of interest

The authors declare that they have no conflict of interest.

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Impact of the Thickness of the Subcutaneous Tissue at the Site of Injection as Measured by Ultrasound on the Therapeutic Response to Subcutaneous anti-Tumour Necrosis Factor Drugs☆

Impacto del grosor del tejido celular subcutáneo en el sitio de la inyección medido por ecografía sobre la respuesta terapéutica a fármacos antifactor de necrosis tumoral subcutáneos

To the Editor,

Biologic therapies with tumor necrosis factor (TNF)-α inhibitors are widely used to treat inflammatory diseases, such as rheumatoid arthritis (RA) and spondyloarthropathies (SpA).[1] They are administered subcutaneously (SC) or intravenously (IV), and the route has an influence on their bioavailability. In SC administration, there are 2 aspects to consider: the site and the injection technique,[2–5] both of which are key factors in the proper administration of the injections; thus, training of patients by the nursing staff is essential for SC self-administration of anti-TNF agents.

The thickness of the subcutaneous tissue (ST) can influence the proper distribution of the drugs throughout the organism. This thickness can be affected by age, sex and body mass index (BMI),[2,4–6] variables that are important for the determination of the administration site and technique for each patient. In the case of insulin-dependent diabetes mellitus, the needles for self-administration devices are available in a wide variety of lengths, depending on the ST thickness, as has been reported previously in a number of publications. However, there are no studies on this subject dealing with rheumatic diseases treated by SC administration of anti-TNF agents. The proper injection technique ensures that the SC anti-TNF agent be injected into ST, rather than intramuscular (IM) or intradermal tissue.

This prospective cross-sectional observational study involved 117 patients with RA (n=59) or SpA (n=58) being treated with an anti-TNF agent that the patients administered SC to themselves for a minimum of 6 months. The thickness of the ST was measured in all the patients at the sites recommended for SC injection (arms, abdomen, thighs), regardless of the preferred site for self-administration, using gray-scale ultrasound (ultrasound system equipped with a 6–18-MHz multifrequency linear transducer). Ultrasound measurement of the ST was always performed using the same method and with the patient in the sitting position. Gel was applied between the probe and the skin to avoid putting pressure on the ST with the probe (Fig. 1). The probe was placed transversely and longitudinally, on the right and left sides, at the sites recommended for SC injection. We then calculated the average between the two measurements.

The results are expressed as the mean ± standard deviation (SD) for continuous variables and as absolute frequencies and percentages for categorical variables. The continuous variables in independent groups were compared using the independent samples *t*-test when 2 groups were involved. For the comparison of 3 groups, we used 1-way analysis of variance (ANOVA) with the Tukey test, or the Kruskal–Wallis test with the Mann–Whitney test and the Bonferroni correction to determine the unpaired samples, depending on the assumption or rejection, respectively, of the null hypothesis. The linear relationship between independent variables was established by means of the Pearson correlation coefficient. Fisher's exact test of independence for categorical variables was applied in the case of 2 dichotomous variables, and the chi-squared test when any of the variables had more than 2 categories. Logistic models were developed as dichotomous outcomes of clinical remission or no clinical remission, according to the Disease Activity Score for 28 joints (DAS28) and C-reactive protein (CRP) level. We analyzed age, BMI, ST thickness in abdomen, arms and thighs, time since diagnosis, time since initiation of anti-TNF therapy (with etanercept, adalimumab, others [because of the small sample size, patients treated with golimumab and certolizumab pegol were analyzed jointly]), and concomitant treatment with disease-modifying antirheumatic drugs. The odds ratio was calculated with its 95% confidence interval). *P* values ≤.05 were considered to indicate significance. The statistical analyses were performed with the SPSS statistical software package (v15.0).

Due to the small sample size, our RA and SpA patients were analyzed jointly, according to the anti-TNF agent utilized. Fifty-nine patients (50.5%) had been diagnosed with RA and 58 (49.5%) with SpA. Fifty-six patients (47.9%) were receiving etanercept; 52 (44.4%), adalimumab; 7 (6%), golimumab; and 2 (1.7%), certolizumab pegol. Eighty-two (70%) self-administered the anti-TNF agent in abdomen, 23 (19.7%) in thigh and 12 (10.3%) in arm.

The majority of the patients were women (n=61, 52.1%). The mean ± SD (range) for the variables were as follows: age, 52.77 ± 13.28 (24–82) years; weight, 74.01 ± 15.19 (46–125) kg; height, 1.65 ± 0.08 (1.43–1.84) m; and BMI, 27 ± 4.75 (18.44–41.58) kg/m^2. The clinical response to the anti-TNF agent was evaluated using the following remission or activity criteria: DAS28 and CRP for the patients with RA and the Ankylosing Spondylitis Disease Activity Score (ASDAS) for the patients with SpA. In RA, remission was considered to be indicated by a DAS28 < 2.6 and no remission by a DAS28 ≥ 2.6, and remission in SpA by an ASDAS < 1.3 and no remission by an ASDAS ≥ 1.3.

The mean thickness of the ST was significantly greater in abdomen (mean ± SD, 24.7 ± 14.3 mm) than in thigh (11.6 ± 4.9 mm) or in arm (9.1 ± 4.5 mm) (*P*<.0005).

The injection site was significantly associated with clinical disease activity measured by DAS28-CRP/ASDAS. The percentage of patients with active disease was significantly higher among those

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