CASE REPORT

Idiopathic chronic polyserositis with massive ascites responding to colchicine in an adult: A case report

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Abstract

Objective: While there are many different causes of ascites, most cases are due to cirrhosis. However, a serum/ascites albumin gradient <1.1 indicates that the ascites is not induced by portal hypertension and mandates a search for other etiologies, including causes of serositis. We describe a 70-year-old patient with persistent ascites and pleuropericarditis who underwent a successful outcome while on colchicine treatment.

Methods: This study was delineated on a case-report basis. Besides supportive care measures, we performed a comprehensive clinical and complementary assessment of the patient, which included laboratory tests, imaging techniques, endoscopic evaluation, full microbiological and pathological studies, diagnostic laparoscopy and thoracoscopy, and genetic testing for autoinflammatory diseases.

Results: Diagnostic workup failed to demonstrate the presence of an underlying etiologic disorder. Large-volume paracentesis was performed once monthly during 13 consecutive months due to painless, massive accumulation of peritoneal fluid. Eventually, colchicine therapy induced a dramatic response with clinical and radiological disappearance of polyserositis within three months of starting on the drug. While on colchicine, the disease has not recurred throughout a thirty two months period of follow-up so far. To our knowledge, the occurrence of idiopathic, chronic refractory ascites and pleuropericarditis resolved under colchicine treatment in an adult not diagnosed with Familial Mediterranean Fever is an exceptional event.

Conclusion: We suggest that in adult patients suffering from idiopathic chronic polyserositis including massive ascites the possible existence of an underlying autoinflammatory condition should be sought. In such a case, a colchicine trial might be regarded as an early suitable therapeutic option.

Keywords

Anakinra, Ascites, Autoinflammatory diseases, Colchicine, Familial Mediterranean fever, Interleukin-1β, Serositis

1 Introduction

Polyserositis is an unspecific disorder that can be induced by infections, neoplasia, connective tissue diseases, medications, and autoinflammatory diseases (AD) such as Familial Mediterranean Fever (FMF). AD, in their turn, may be considered as primary disorders of the innate immunity that are characterized by the hyperactivation of antigen-independent inflammatory mechanisms in the absence of infection or autoantibodies production [1-3]. AD usually presents with recurrent episodes of fever and systemic inflammation affecting eyes, skin, joints, and serosal surfaces [2]. Because overproduction of interleukin (IL)-1β is thought to be the mechanism responsible for disease manifestations, nearly all AD are characteristically responsive to IL-1β blockade [2]. Although the existence of an autoinflammatory disease can be confirmed be means of genetic testing [4-6], a delay in diagnosis is frequent due to the rarity and non-pathognomonic features of these disorders [7]. In addition, it is well known the spectrum of AD is permanently growing due to the discovery of distinct genetic mutations that underlie these entities [3, 8]. We describe a case of chronic polyserositis in an adult patient that included massive ascites and pleuropericardial involvement. Even though an exhaustive diagnostic workup, including genetic study, rendered no definitive clues to the etiology, outcome was successful under colchicine therapy.

2 Case presentation

A 70-year-old man presented to our hospital in December 2010 with a 2-month history of painless, progressive abdominal distension. His past medical history was unremarkable except for arterial hypertension and diabetes mellitus, which were well controlled with ramipril and gliclazide, respectively. He denied alcohol or other drugs consumption. On admission, he appeared to be in a good health status. The blood pressure was 120/70 mmHg, the heart rate was 80/min, and the temperature was 36°C. Jugular venous pressure was normal. His lungs were clear and his heart sounds were normal. Abdominal examination revealed a tense ascites without rebound tenderness and normal bowel sounds. There was no organomegaly, palpable lymphadenopathy, peripheral edema, rash, skin nodules, or other striking physical findings.

Initial laboratory results were significant for high erythrocyte sedimentation rate (ESR) and increased serum level of C-reactive protein (CRP) (see Table 1). Electrocardiogram and chest-x ray were normal. Abdominal ultrasonography revealed the presence of massive ascites, the liver, spleen, kidneys, and pancreas being normal. Doppler ultrasound examination of the portal and hepatic venous systems was also unexceptional, without evidence of portal hypertension or Budd-Chiari syndrome typical characteristics. Computed tomography (CT) scan of the thorax, abdomen, and pelvis, obtained after the oral and intravenous administration of contrast material, showed pericardial thickening without pericardial effusion, mild bilateral pleural effusion, and massive accumulation of ascitic fluid but no thickening or opacification of mesentery, omentum or peritoneum. There was no organomegaly and lymph nodes were not enlarged.

Table 1. Relevant laboratory results at presentation

Variable	Value
Blood	
White-cell count	$5.6 \times 10^3/mm^3$ (normal, 4.5-11)
Hemoglobin	11.9 g/dL (12-18)
Platelet count	$300 \times 10^3/mm^3$ (150-450)
Erythrocyte sedimentation rate	45 mm/ hour (2-30)
Glucose	92 mg/dL (76-110)
Urea nitrogen	19.6 mg/dL (4.66-23.3)
Creatinine	0.69 mg/dL (0.5-1.15)
Aspartate aminotransferase	18 U/L (0-37)
Alanine aminotransferase	16 U/L (5-41)

(Table continued on Page 46)

Table 1. (continued)

Variable	Value
Alkaline phosphatase	8 U/L (40-129)
Gamma-glutamyltransferase	15 U/L (8-61)
Lactate dehydrogenase	135 U/L (135-250)
Total bilirubin	0.3 mg/dL (0.1-1.2)
Proteins	6.1 g/dL (6.2-8.4)
Albumin	3 g/dL (3.5-5.1)
Serum/ascites albumin gradient	0.5 g/dL
C-reactive protein	6.68 mg/dL (<0.5)
Serum iron concentration	31 μg/mL (59-158)
Transferrin saturation ratio	13 % (20-50)
Serum ferritin	121 ng/mL (16-300)
Rheumatoid factor	22.6 UI/mL (<14)
Antinuclear antibodies titer	<1/80 (negative*)
Antineutrophil cytoplasm antibodies	Negative
Carcinoembryonic antigen	0.4 ng/mL (0.1-5)
Alpha fetoprotein	1.9 ng/mL (1-7)
Hbs Ag, anti-HBs, anti-HBc, anti-HCV	Negative
HIV serology	Negative
Urine	
Proteinuria	10.4 mg/day (<150)
Peritoneal Fluid	
Glucose	113 mg/dL
Proteins	4.9 g/dL
Albumin	2.5 g/dL
Lactate dehydrogenase	290 UI/L
Adenosine deaminase	26.2 U/L
Amylase	32 UI/L
White-cell count	300 /mm3
Lymphocytes	240 /mm3
Red blood cell count	250 /mm3
Triglycerides	20.4 mg/dL
Total bilirubin	0.3 mg/dL
Carcinoembryonic antigen	0.37 ng/mL
Pleural Fluid	
Glucose	114 mg/dL
Proteins	5.1 g/dL
Lactate dehydrogenase	99 UI/L
Adenosine deaminase	24 U/L
Cholesterol	150 mg/dL
Triglycerides	21 mg/dL
Amylase	34 UI/L

Note. *In our reference laboratory titers below 1/160 are considered negative

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Large-volume paracentesis was done at that time, with evacuation of around 8 liters of normally colored ascitic fluid. Peritoneal fluid assessment displayed the presence of exudative ascites with a serum/ascites albumin gradient of 0.5 g/dL and a high percentage of lymphocytes (80%); no acid-fast bacilli, other microorganisms, or malignant cells were detected (see Table 1). Serology for HIV, HCV and HBV as well as tuberculin skin test were negative. Antinuclear antibodies and other autoantibodies were also negative. Proteinogram was normal and serum level of immunoglobulins, complement, and ferritin were within normal limits. Urine testing did not reveal microscopic hematuria or proteinuria.

Due to diagnostic uncertainty, laparoscopy was performed and liver and peritoneal biopsies were obtained. Except for ascites, nothing conspicuous was seen throughout the surgical procedure. Histopathological study of biopsy samples revealed unspecific chronic inflammation of the peritoneum, no liver abnormalities, and absence of neoplastic cells, microorganisms, or granulomas. An ensuing videothoracoscopy let a lymphocytic pleural exudate be drained; pleural biopsy also demonstrated nonspecific chronic inflammation with neither tumor cells nor other abnormal findings. Inmmunohistologic study of ascitic and pleural fluid showed normal features. Upper gastrointestinal endoscopy, colonoscopy, and capsule endoscopy exploration were normal, polymerase chain reaction assay for *Tropheryma whipplei* was negative in duodenal biopsy samples, and amyloid protein deposition was not identified on rectal biopsy specimens. Bone marrow examination turned out to be normal. Echocardiography and cardiovascular magnetic resonance (CMR) imaging revealed pericardial thickening (5.5 mm) with neither pericardial effusion nor signs of constrictive pericarditis; both of them were otherwise unremarkable. Positron emission tomography revealed no uptake abnormalities. Culture of samples from peritoneal and pleural fluid and tissues and bone marrow grew neither *Mycobacterium tuberculosis* nor other pathogens. He was screened for mutations causing AD, including assessment of exons 1 to 10 in *MEFV* gene (linked to Familial Mediterranean Fever, FMF), exons 2 to 7 in *TNFRSF1A* gene (related to tumor necrosis factor receptor-associated periodic syndrome, TRAPS), exons 1 to 10 in *MVK* gene (associated with Hyper-IgD syndrome), exons 1 to 9 in *CIAS1* gene (linked to cryopyrin-associated periodic syndromes), and exon 4 in *NOD2* gene (related to Blau syndrome/early-onset sarcoidosis), the result being negative for all of them.

Following hospital discharge, the patient had monthly paracentesis of around 7 liters/session carried out because of gradual reappearance of tense ascites, but he has never developed fever, abdominal or chest pain, rash, arthralgia/arthritis, or ocular symptoms, and has remained otherwise symptom-free. Given that serum interferon gamma test for *M. tuberculosis* turned to be positive, the presence of lymphocytosis in peritoneal and pleural fluid, and the absence of a specific etiology, he was put on empirical antituberculous treatment with isoniazid, rifampicin, and ethambutol in May, 2011. Within the second month of therapy he developed liver injury (ALT 435 UI/L, AST 281 UI/L, GGT 30 UI/L, ALP 67 UI/L, TB 0.2 mg/dl). Afterwards, tuberculostatic agents were stopped and liver biochemistry abnormalities quickly resolved. In September 2011, prednisone was started (40 mg daily as initial dose) bearing in mind a hypothetic, underlying systemic inflammatory disorder. Frequency of paracentesis was slightly reduced and we decided to add colchicine in January, 2012 (1 mg twice a day) with gradual tapering of the prednisone dose until it was discontinued in February 2012. Within three months after initiation of colchicine therapy, ascites, pleural effusion, and pericardial thickening disappeared and the dose of the drug was decreased up to 1 mg daily. At follow-up thirty two months after starting colchicine regime, the patient goes on symptomless and imaging studies (abdominal ultrasonography and CMR) as well as laboratory results reveal no abnormalities.

3 Discussion

This clinical observation refers to a 70-year-old man suffering from chronic polyserositis that involved peritoneum (massive ascites), pleura, and pericardium. All diagnostic procedures that were carried out let us exclude infectious, malignant, granulomatous, metabolic, and autoimmune diseases but failed to ascertain the etiology of his illness. Specifically, our patient did not fulfill the criteria for being diagnosed with FMF or other currently recognized autoinflammatory diseases. Although there was a favorable response to colchicine (1 minor criterion, see Table 2; 1 major criterion, see Table 3) and laparotomy was negative (1 supportive criterion, see Table 2), FMF diagnosis could not be

established because he did not meet the other required criteria. Even though the possibility of a connective-tissue disease was also considered, the patient did not fulfill classification criteria for systemic lupus erythematosus or for any other connective-tissue diseases. Nevertheless, since the patient had elevated rheumatoid factor levels, an attractive possibility could have been that the clinical features were the expression of extra-articular manifestations of rheumatoid arthritis (RA). In this regard, in some cases of RA extra-articular involvement prevails over joint manifestations and, certainly, the systemic involvement of RA includes the presence of pericarditis and pleuritis. However, the patient did not have rheumatoid nodules and the occurrence of peritonitis appears to be very unlikely in the setting of RA. In addition, although low serum Fe and transferrin, anemia, high ESR, and even higher CRP can be observed in patients with inflammatory arthritis like RA, no clinical evidence of synovitis involving peripheral joints of hands and feet that is typical of RA was observed. Finally, and according both to the 2010 American College of Rheumatology (ACR)/European League Against Rheumatism and to the 1987 ACR classification criteria [9-11], our patient did not meet the criteria for RA diagnosis.

Table 2. Criteria for the diagnosis of familial Mediterranean fever (FMF) (adapted from reference [6])

Major criteria
Typical attacks*
1. Peritonitis (generalized)
2. Pleuritis (unilateral) or pericarditis
3. Monoarthritis (hip, knee, ankle)
4. Fever alone
Minor criteria
1-3. Incomplete attacks** involving ≥1 of the following sites
1. Abdomen
2. Chest
3. Joint
4. Exertional leg pain
5. Favorable response to colchicine
Supportive criteria
1. Family history of FMF
2. Appropriate ethnic origin
3. Age < 20years at disease onset
4-7. Features of attacks
4. Severe, requiring bed rest
5. Spontaneous remission
6. Symptom-free interval
7. Transient inflammatory response, with ≥1 abnormal test result(s) for: white blood cell count, erythrocyte sedimentation rate, serum amyloid A, and/or fibrinogen
8. Episodic proteinuria/hematuria
9. Negative laparotomy or removal of normal appendix
10. Consanguinity of parents

Note. ***Typical attacks:*** recurrent (≥3 of the same type), febrile (≥38 °C), and short (lasting between 12 hours and 3 days**) **Incomplete attacks**: painful and recurrent attacks that differ from typical attacks in 1 or 2 features, as follows: 1) temperature ≤38ºC; 2) shorter or longer attacks than specified (but not <6 hours or >1 week); 3) no signs of peritonitis; 4) localized abdominal pain; 5) arthritis in joints other than those aforementioned. **FMF diagnosis requires**: ≥ 1major criterion, or ≥ 2 minor criteria, or 1 minor criterion plus ≥ 5 supportive criteria, or 1 minor criterion plus ≥ 4 of the first 5 supportive criteria.

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Table 3. Tel-Hashomer criteria for familial Mediterranean fever (FMF) diagnosis [5]

Major Criteria
1. Recurrent febrile episodes accompanied by peritonitis, synovitis, or pleurisy
2. Amyloidosis of AA-type without a predisposing disease
3. Favorable response to colchicine treatment
Minor Criteria
1. Recurrent febrile attacks
2. Erysipelas-like erythema
3. FMF in a first-degree relative

Note. A FMF diagnosis requires 2 major criteria or 1 major plus 2 minor criteria.

Serosal involvement may occur in the setting of systemic inflammatory disorders such as adult-onset Still's disease (AOSD) [12], an entity in which laboratory testing and histological features are nonspecific. Accordingly, its diagnosis should rely on clinical suspicion and is often supported by the use of classification criteria [12, 13]. The classic presentation of AOSD includes fever, a 'salmon-pink' rash, arthralgia, arthritis, and lymphadenopathy while serositis and other atypical manifestations are seldom reported and are considered not to be major diagnostic criteria [12-15].

FMF and TRAPS may present with serosal involvement too. Both are inherited diseases, characterized by recurrent episodes of fever with serositis and other acute manifestations [5, 6, 16-19]. In 1997, the cloning by two independent consortia of the gene responsible for FMF, named *MEFV*, located on the short arm of the chromosome 16, made genetic testing of this condition possible [20, 21]. Several *MEFV* mutations were initially identified in exon 10, and accounted for approximately 75% of FMF cases [20, 21]. Subsequently, additional mutations have been found in exons 10, 3, 2, and 5, most of them being less common and manifested by different phenotypic expressions [16]. To date, there are approximately thirty mutations in the *MEFV* gene. Regrettably, identifiable mutations are still lacking in at least 20% of cases with clinically defined FMF [16]. On the other hand, the diagnosis of TRAPS can also be confirmed by genetic testing for common mutations in the *TNFR1* gene [17].

FMF and TRAPS are disorders usually described in the pediatric age [5, 17]. However, a late onset of the disease has also been reported for both entities, with 14%-30% of patients manifesting FMF in late adulthood up to the age of 65 [5, 22, 23], and some cases of TRAPS appearing up to the age of 63 years [17]. Late onset cases present as a milder disease and they are frequently related to low-penetrance mutations [22]. Adult-onset FMF and TRAPS patients may develop atypical manifestations, including recurrent serosal involvement as the only clinical feature [18, 24, 25]. In addition, cases of FMF presenting only with ascites (even massive) as the first sign of disease have been reported [26, 27]. As already commented about all the aforementioned disorders, our case did not fulfill either TRAPS diagnostic criteria [17].

When there is no genetic confirmation, as in our case, the diagnosis of FMF should rely on clinical grounds. The most commonly used criteria are those by Tel-Hashomer and Livneh, each of them with a sensitivity and specificity >95% and both validated in a population with high prevalence of FMF [5, 6]. Unfortunately, there are no established clinical criteria for communities with intermediate prevalence as the Spanish population. Our patient had polyserositis (confirmed in pleura and peritoneum by pathological examination) along with increased serum levels of inflammatory markers (ESR, CRP), unproductive laparoscopic and thoracoscopic study, and favorable response to colchicine. However, he did not develop the characteristic recurrent attacks of this disease (with or without fever), with symptomless periods that are required to make a definite diagnosis of FMF (see Table 2).

Since FMF is uncommon in Spain, it is possible the clinical spectrum of the disease may be somehow different from that described in regions with higher prevalence of this condition. Keeping in mind the absence of infectious, malignant, or autoimmune diseases, the favourable outcome following colchicine therapy, the inexistence of pathognomonic diagnostic clues for FMF, and the fact that adult-onset FMF may have uncommon presentations with relatively high number of patients lacking *MEFV* mutations identified, we think our case could be labeled as a FMF-like autoinflammatory syndrome. However, we cannot definitely rule out the possibility of a distinct autoinflammatory disorder, in view of our

patient has never developed the characteristic episodic attacks of FMF. Further investigation seems to be required to improve the diagnostic accuracy of classification criteria in countries with low prevalence of FMF and to expand the current understanding of the genetic basis, clinical manifestations, and treatment of AD.

Concerning patient management, our purpose is to maintain colchicine therapy in a low dose of 1 mg/day for the prevention of disease recurrence during an additional four month period, then tapering slowly off the drug (ideally until withdrawal) while trying to keep the disorder under control. Appropriate monitoring including blood cell count and hepatic as well as renal function tests will be conducted every 6 months. If there is disease recurrence or relapse in spite of colchicine therapy or if potential side effects related to the drug occur (e.g., gastrointestinal complaints, headache, fatigue, pharyngolaryngeal pain, dermatosis, hepatotoxicity, blood dyscrasias, or myopathy [28]), treatment with IL-1 receptor inhibitor anakinra will be considered as a suitable therapeutic option [29]. On the other hand, the fact that our patient received 6 months of prednisone, with some overlap with colchicine (2 months), should be acknowledged. In this regard, couldn't the salutary response attributed to colchicine have been due to the prednisone, with some delayed effect of that glucocorticoid? Prednisone is readily absorbed from the gastrointestinal tract and is then converted to its active metabolite prednisolone in the liver. The plasma half-life of prednisone and prednisolone is about 60 minutes and 2-4 hours, respectively. Taking into account these considerations and that prednisone was discontinued in January 2012, it seems to be highly improbable that the ongoing, favorable clinical, laboratory, and radiological outcome observed in our patient could be attributed to corticotherapy.

To sum up, we suggest that in adult patients with idiopathic chronic polyserositis including massive ascites early colchicine treatment might be regarded as an appropriate management option. Such an approach could result more cost-effective and potentially less harmful than other therapeutic alternatives.

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