Coexisting Microscopic Polyangiitis, Primary Biliary Cirrhosis, Renal Tubular Acidosis And Tubular Phosphate Leak

M Varsavsky, J Callejas-Rubio, D Sánchez-Cano, N Ortego-Centeno, T Caballero-Morales

Citation

M Varsavsky, J Callejas-Rubio, D Sánchez-Cano, N Ortego-Centeno, T Caballero-Morales. *Coexisting Microscopic Polyangiitis, Primary Biliary Cirrhosis, Renal Tubular Acidosis And Tubular Phosphate Leak*. The Internet Journal of Gastroenterology. 2008 Volume 7 Number 2.

Abstract

Primary biliary cirrosis is a disease frequently associated with different autoimmune disorders, and whose clinical manifestations can precede to those of liver involvement. We report a case of atypical presentation in the form of vasculitis, together with microscopic polyangiitis criteria and subsequent development of incomplete renal tubular acidosis and phosphate transtubular leak. We believe this association to be first described in literature.

INTRODUCTION

Primary biliary cirrhosis (PBC) is a slowly progressive, chronic liver disorder characterized by a non-supurative chronic cholangitis. 95% of patients are women, rarely occurring before the age of 30([1]). It is often associated with different autoimmune diseases, such as Sjögren's syndrome, scleroderma and rheumatoid arthritis ([8]). Development of renal tubular acidosis (RTA) or vasculitis is more infrequent. RTA refers to an impaired reabsorption of the filtered bicarbonate and / or hydrogen ion excretion, resulting in a normal anion gap (hyperchloremic) metabolic acidosis with a relatively preserved glomerular filtration. There are four subgroups of RTA, being type 1 or distal and type 2 or proximal the most common ones. Both of them can present as either an inherited or acquired condition, autoimmune disorders being found among the causes of type 1([2]). Microscopic polyangiitis (MPA) is a systemic necrotising vasculitis of the capillaries, venules and arterioles, and occasionally medium and small sized arteries ([3]). We present an unusual case of association of MPA, PBC and renal tubular acidosis with phosphate leak.

CASE REPORT

A 30-year-old male with a history of allergic rhinitis and bronchial hyperreactivity presented with acute appendicitis, confirmed after appendectomy and pathological study of the specimen obtained. The patient remained febrile during the postoperative period, developing paralytic ileus and acute renal failure, requiring an exploratory laparotomy on the fourth day. Small bowel was considerably dilated, and abundant serous exudates could be found within the abdominal cavity. 48 hours afterwards, fever persisted, and serohematic diarrhea appeared. Blood and stool cultures were all negative, as well as study for Clostridium Difficile. A colonoscopy study was performed up to 40 cm from anal margin, due to severe edema. Rectal mucous was intensely erythematosus with haemorrhages and diffuse small ulcerations. Biopsy was consistent with non-specific proctitis (Fig. 1). Subsequently, a radionuclide imaging scan with HMPAO-marked leukocytes showed minimum inflammatory activity on the left flank. High-dose metilprednisolone therapy was then started, which was followed by an improvement of fever and diarrhea. On the 20 th day of admission, pain on the right-upper-quadrant together with signs of peritoneal irritation developed, following steroids tapering. A new exploratory laparotomy was performed, revealing acute cholecystitis and two intestinal perforations, and so cholecystectomy and intestinal resection were required. A new exploratory laparotomy was needed 48 hours afterwards, due to surgical wound dehiscence, during which an intra-operative colonoscopy was performed, featuring a multiply ulcerated colonic mucous. Pathological study of the small bowel revealed multifocal ulcerations of the mucous with perforation

secondary to segmentary vascultitis with fibrinoid necrosis involving small arteries and some medium sized ones (fig1). Gallbladder findings were consistent with gangrenous cholecystitis with vasculitis phenomena similar to those observed in the small intestine (fig. 2).

Figure 1

Figure 1: Section of small bowell wall: the mucosa is ulcerated and a medium-sized submucosal arteria shows fibrinoid necrosis with partial thrombosis (arrow) (hematoxilin-eosin, original magnification, 4x). L= lumen; M=muscle layer.

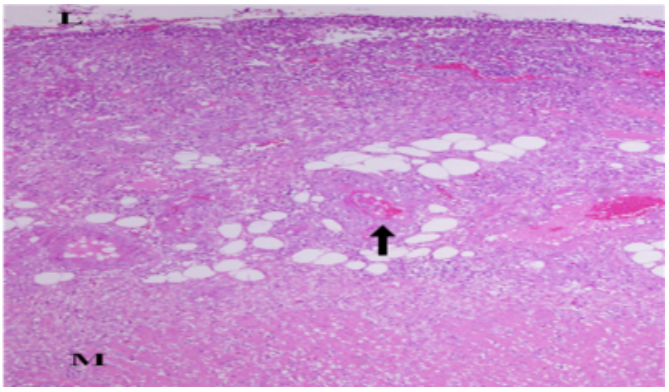
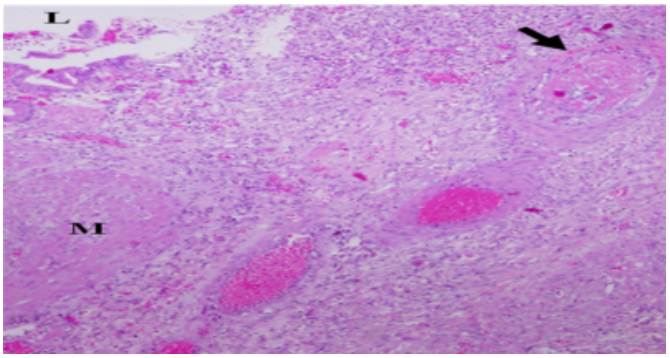


Figure 2

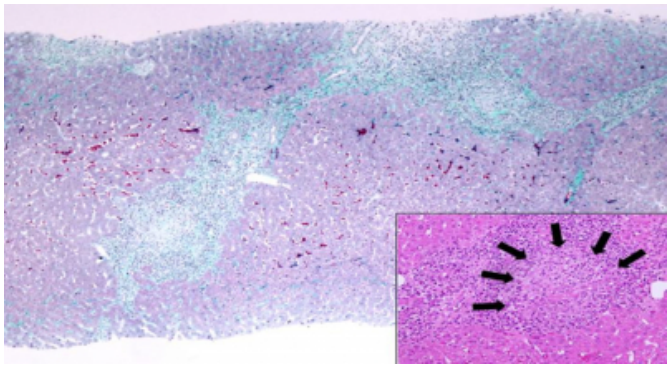
Figure 2: Gallbladder wall: the mucosa is partially ulcerated and a thrombosed arteria (arrow) is obseved (hematoxilin-eosin, original magnification 4x). L= lumen; M= muscle layer.



Colonic mucous showed round ulcers of 0.5-1 cm in diameter, with erythematous borders and fibrinoid base, which might be attributed to vasculitis. Blood tests findings were as follows: hemoglobin 12.1 mg/dl; hematocrit 36.1%; white blood cell count 13700/mm ^{3} ; platelets 229000/mm ^{3} ; erythrocyte sedimentation rate 20 mm/h; C reactive protein 0.5 mg/dl; glucose 88 mg/dl; urea nitrogen 45.3 mg/dl; creatinine 1,7 mg/dl; total bilirubin 1.3 mg/dl; alanine aminotransferase (ALT) 85 U/L (N<40U/L); aspartate aminotransferase (AST) 30 U/L (N<37U/L); alkaline phosphatase 191 U/L (N 40-130 U/L); gamma glutamyl transpeptidase 140 U/L (N 7-32 U/L); sodium 143 mEq/l; potassium 4.9 mEq/l. Serologies for VHB, VHC, VHA, EBV, CMV and HIV were all negative. Rheumatoid factor, crioglobulines, ANA, ACA and lupus anticoagulant were negative, too. Perinuclear ANCA were positive, titre 1:160. A diagnose of MPA was then established, and thus cyclophosphamide boluses (500 mg intravenously every 15 days) were started, fever disappearing and no other events occurring. Due to persistently abnormal liver function tests, ultrasound imaging was performed, only revealing a slightly enlarged liver. Antimitochondrial antibodies were positive, titre 1:640, meanwhile antibodies against parietal cells, anti-smooth muscle antibodies and liver-kidney microsomal antibodies were all negative. Liver biopsy showed periportal inflammation along with ductal damage and bridging fibrosis, consistent with PBC stage three (fig. 3). Liver tests normalised after ursodeoxycholic acid (15 mg/kg per day) was added to therapy.

Figure 3

Figure 3: Liver biopsy with bringing fibrosis and porto-periportal inflammation (Gomori's trichrome, original magnification 4x). Inset: detail of a portal tract with a biliary duct partially damaged and surrounded by histiocytic cells (arrows), a tipical lesion of Primary Biliary Cirrhosis (Hematoxilin-eosin, original magnification 10x)



Two years afterwards, hypophosphatemia (1.2 mg/dl, N:2.5-5) developed. Laboratory findings showed the following results: urea nitrogen 15 mg/dl; creatinine: 1,4 mg/dl; serum calcium 9,8 mg/dl (N: 8,5-10,5), sodium 140 mEq/l (N: 135-145), potassium 4 mEq/l (N: 3,5-4,5); chloride: 105 mEq/l (N: 94-111); magnesium:1,5 mg/dl (N: 1,5-2.5 mg/dl), phosphaturia: 1350 mg/day ; magnesiuria 2,2mg/dl; urine pH 6,5; positive urine anion gap; phosphate tubular reabsorption 47% (N: 75-90%); PTH 40 pg/ml (N: 10-55) and 25-hydroxyvitamin D 25 ng/ml (N: 9-30); negative urine culture. Incomplete RTA with phosphate leak

was diagnosed and phosphate oral supplements were added to treatment.

DISCUSSION

PBC is a chronic disorder with an insidious onset, which is usually suspected after abnormal liver function tests preformed routinely ([8]). On the other hand, since it is associated to other autoimmune diseases in 30% of cases - such as thyroid disorders, CREST syndrome (5-15%), Sjögren's syndrome (40-60%), Raynaud phenomenon, rheumatoid arthritis (5-10%), celiac disease, bowel inflammatory disease, dermatomyositis, systemic erythematosus lupus, or haemolytic anemia- it occurs that their clinical features frequently precede those directly associated with PBC([13]).

The case reported atypically presented in form of vasculitis. Association with vasculitis involving differently sized vessels has rarely been described, including Churg-Strauss syndrome, Wegener's granulomatosis (WG), giant cell arteritis and Goodpasture's syndrome ([7,8]), and only recently, MPA ([5]). Many authors associate MPA with WG, due to the fact that they share positivity to ANCA (70% cases in MPA) as well as similar therapy outcomes. However, these ANCA react with myeloperoxidase in MPA (perinuclear ANCA) whereas they do with proteinase 3 (cytoplasmic ANCA) in WG ([11, 20]). Nonetheless, MPA has recently been recognised as a differentiated entity from classical polyarteritis nodosa, in which ANCA are usually negative and vessels involved are predominantly those of medium size ([20]). The most frequent clinical features of MPA are necrotising glomerulonephritis and pulmonary hemorrhage. Other manifestations can be found, such as livedo reticularis, fever, artharlgia, arthritis, digital ischemia, multiple mononeuritis, pneumonitis, pleurisy, and more infrequently, gastrointestinal involvement (intestinal infarction, intestinal ulcerations, intestinal perforation, cholecystitis, appendicitis, pancreatitis) ([3, 15, 17]). Intestinal involvement is present in less than 20% of MPA patients, generally being a poor prognosis sign ([14, 16]).

Several models have been proposed to explain the relationship between PBC and vasculitis, among them, association with certain HLA antigens ([10, 19]). None of these mechanisms, though, have clearly been established. Perinuclear ANCA are generally associated with vasculitis, but they can be positive in other autoimmune disorders, too, such as systemic lupus erythematous, rheumatoid arthritis, Crohn's diseases and autoimmune hepatic disorders. More specifically, they are positive in 25-30% cases of PBC, thus suggesting a possible role in the pathogenesis of this association ([18]).

Incomplete RTA has been described in several cases of PBC ([4, 6,12]). Different studies have found that 33-50% of PBC patients present with either latent or incomplete renal acidosis, without nephrocalcinosis (usually in RTA type 1) or systemic involvement, which is only made evident by alkali infusion ([2, 6, 12]). Association between PBC and RTA might be the result of a damaged distal renal tubule as a consequence of an increased copper excretion in PBC patients as the disease progresses. Or else, it could be due to immunological abnormalities, such as circulating immune complexes, a variety of auto antibodies and highly activated complement system ([4,6,9,12]). RTA in our patient resulted in a hypophosphatemia as a consequence of a phosphate renal leak. There are cases published of nephrotoxicity for ifosfamide in children but in all the cases associated with glycosuria and / or aminoaciduria, thing that does not happen in our case ([21]).

In conclusion, our case shows in a passionate way how PBC can be associated to different autoimmune disorders, and so, how closely they should be followed so as to rule them out early in time. On the other hand, hypophosphatemia in a PBC patient should raise suspicion of a RTA, and proper metabolic evaluation should be undertaken to confirm it.

References

1. Iannone F, Falappone P, et al. Microscopic polyangiitis associated with primary biliary cirrhosis. J Rheumatol. 2003;30(12):2710-2.
2. Lino M, Binaut R, et al. Tubulointerstitial Nephritis and Fanconi Syndrome in Primary Biliary Cirrhosis. Am J Kidney Dis 2003;46(3): e41-6.
3. Diederichsen H, Sorensen PG, et al. Petechiae and Vasculitis in Asymptomatic Primary Biliary Cirrhosis 1985;65:263-266.
4. Toblli J, Findor J, et al. Latent distal renal tubular acidosis in primary biliary cirrhosis and chronic autoimmune hepatitis. Acta Gastroenterol Latinoam 1993; 23:235-238.
5. Terkeltaub JM, Esdaile C, et al. Vasculitis as a presenting manifestation of primary biliary cirrhosis: a case report. Clin Exp Rheumatol 1984;2(1):67-73.
6. Rodriguez Soriano J. Renal Tubular Acidosis: The Clinica Entity. J Am Soc Nephrol 2002;13:2160-2170.
7. Pares A, Rimola A, et al. Renal Tubular Acidosis in Primary Biliary Cirrhosis. Gastroenterology 1981;80:681-6.
8. Talwalkar JA, Lindor KD. Primary biliary cirrhosis. Lancet 2003;362:53-61.
9. Konishi K, Hayashi M, et al. Renal tubular acidosis with autoantibody directed to renal collecting-ducts cells. N Engl J Med 1994;331:1593-4.
10. RC, Dickson ER, et al. Immune complexes in primary

biliary cirrhosis. Higher prevalence of circulating immune complexes in patients with associated autoimmune features. Am J Med 1982;73:192.
11. Guillevin L, Durand-Gasselin B, et al. Microscopic polyangiitis: clinical and laboratory findings in eighty-five patients. Arthritis Rheum 1999;42:421-430.
12. Izumi N, Hasuramura Y, et al. Hypouricemia and hyperuricosuria as expressions of renal tubular damage in primary biliary cirrhosis. Hepatology 1983;719-723.
13. Newton JL; Nij Bhala et al. Characterisation of the associations impact of symptoms in primary biliary cirrhosis using a isease specific quality of life measure. J Hepatol 2006; 44:776-783.
14. Pagnoux C, Mahr A et al. Presentation and outcome of gastrointestinal involvement in systemic necrotizing vasculities. Medicine (Baltimore) 2005;84:115-128.
15. Komanduri S, Jakate S et al. Focal rectal capillaritis: microscopic polyangiitis presenting as painless rectal bleeding. J Clin Gastroenterol 2002;35:157-9.
16. Shigehiko U, Masami M et al. Microscopio polyangiitis complicated with massive intestinal bleeding. J Gastroenterol 2001;36:264-270.
17. Tsai CN, Chang CM et al. Extended colonic ulcerations in a patient wih microscopic polyangiitis. Ann Rheum Dis 2004;63:1521-1522.
18. Kallenberg C, Leontine Mulder A et al. Antineutrophil cytoplasmic antibodies: a still-growing class of autoantibodies in inflammatory disorders. Am J Med.1992;93:675-682.
19. Harada N, Dohmen K et al. Sibling cases of primary biliary cirrhosis associated with polymiositis, vasculitis and Hashimoto´s thyroiditis. Internal Medicine 1992;31:289.293.
20. Jennette JC, Falk RJ, Andrassy K, Bacon PA, Churg J, Gross WL, Hagen EC, Hoffman GS, Hunder GG, Kallenberg CG, et al. Nomenclature of systemic vasculitides. Proposal of an international consensus conference. Arthritis Rheum. 1994 Feb;37(2):187-92.
21. Skinner R, Pearson AD, English MW et al. Risk factor for ifosfamide nephrotoxicity in children. Lancet. 1996;346:578-580.

Author Information

Mariela Varsavsky, MD
Endocrinology and Nutrition Department, University Hospital San Cecilio

José Luis Callejas-Rubio, MD
Systemic Autoimmune Diseases Unit, University Hospital San Cecilio

Daniel Sánchez-Cano, MD
Systemic Autoimmune Diseases Unit, University Hospital San Cecilio

Norberto Ortego-Centeno, MD
Systemic Autoimmune Diseases Unit, University Hospital San Cecilio

Trinidad Caballero-Morales, MD
Pathology Department, University Hospital San Cecilio