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CASE REPORT

Multi-organ involvement and intratubular calcium phosphate deposition in the kidney biopsy: what should we investigate?

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Abstract

Background Anorexia nervosa is frequently associated with alcohol use disorder. Both of them may adversely affect almost every body system, leading to worse clinical outcomes and high mortality risk. Nonetheless, there is little evidence interrelating anorexia nervosa, alcohol use disorder, and kidney failure.

Case We report a case of a 30-year-old male with multi-organ involvement at admission, including pancytopenia, electrolyte alterations, impaired liver function, and renal failure. The kidney biopsy revealed calcium phosphate crystalline nephropathy and IgA nephropathy. The bone marrow biopsy and aspiration showed a hypocellular bone marrow and a focal spindle cell infiltrate with atypical vascular proliferation. Nonspecific liver disease was revealed by ultrasound. Further investigation was performed, uncovering a possible masked diagnosis of anorexia nervosa and alcohol use disorder. With the restoration of adequate nutrition and the withdrawal of possible external triggers, a partial recovery was achieved.

Conclusions Anorexia nervosa and alcohol use disorder may promote tissue injury, including kidney failure, specifically calcium phosphate crystalline nephropathy and IgA nephropathy. This multi-organ involvement may lose its reversibility if anorexia nervosa and alcohol use disorder remain persistent. An early diagnosis and a successful multidisciplinary approach may prevent life-threatening complications.

Level of evidence Level V, case report.

Keywords Anorexia nervosa · Calcium phosphate crystalline nephropathy · Alcohol use disorder · IgA nephropathy · Liver disease · Pancytopenia

Introduction

Anorexia nervosa (AN) has been defined, following the DSM-5 guidelines [1], by these diagnostic criteria (all of them): a restriction of energy intake relative to requirements leading to significantly low body weight, an intense fear of gaining weight or becoming fat, and a disturbance in the way in which one's body weight or shape is experienced. Two subcategories have been specified: the restricting type (without binge eating), and the binge eating/purging type (where the person regularly engages in binge eating and purging behaviors, such as self-induced vomiting and/or the misuse of laxatives or diuretics). AN typically begins in early-to-mild adolescence, the sex ratio in adults is 1:8 (with more females affected), and it is an important cause of physical and psychosocial morbidity [2].

Alcohol use disorder (AUD) has been defined by the DSM-5 guidelines as a problematic pattern of alcohol use that leads to clinical impairment or distress, occurring within 12 months, and including some characteristics, such as consumption of large amounts of alcohol or over a longer period than was intended, unsuccessful efforts to cut down alcohol use, promoting activities for alcohol consumption, tolerance to large amounts of alcohol to achieve

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intoxication, continued use of alcohol despite having persistent or recurrent social problems exacerbated by alcohol effects, among others [1]. AUD can be mild, moderate, or severe, and according to the National Institute on Alcohol Abuse and Alcoholism, its prevalence in the USA is estimated at 1.7% of the age group 12–17 years old, and at 5.6% among adults of 18 years and older. AUD is considered a brain disorder and it can promote other comorbidities such as cardiomyopathy, cerebrovascular disease, hypertension, malnutrition, alcoholic hepatitis and cirrhosis, cytopenias, and pancreatitis. Binge drinking or heavy drinking is defined by the National Institute on Alcohol Abuse and Alcoholism as a pattern of drinking alcohol that raises a person's blood alcohol concentration to at least 0.08% in about 2 h (which amounts to consuming five alcoholic drinks for men and four alcoholic drinks for women) [3]. Although it is the most common form of alcohol misuse in adolescents and young adults, it is insufficient to meet the criteria for an AUD diagnosis.

Several studies observed that patients with an eating disorder, including AN, are at risk for substance use disorders, especially AUD, than the general population over a prolonged period [4]. This association carries worse clinical outcomes and increases the mortality risk of these patients.

In the USA and other developed countries, the most common diagnostic groups of renal disease that appear in people younger than 30 years old are congenital anomalies of the kidneys and the urinary tract, chronic glomerulonephritis, and renal cystic ciliopathies, which together encompass > 70% of early-onset chronic kidney disease (CKD) diagnoses [5]. Secondary nephropathies present a low incidence in young adults. AUD and AN, as we have already mentioned, are well-known risk factors for tissue injury and are frequently associated with malnutrition, which may favor kidney injury [2, 6]. Nonetheless, we have to remark that the link between AN, AUD, and kidney injury is intriguing and controversial. There is little evidence interrelating AN, AUD, and kidney failure.

Case presentation

A 30-year-old male was admitted to the nephrology department from our hospital with renal failure. He referred to occasional alcohol intake and presented with no family history of kidney disease or other relevant pathologies. We did not have previous blood test results.

Upon admission, the patient complained of asthenia in the last 3 weeks, without any other associated symptoms. The physical examination revealed a body mass index (BMI) of 16.4 kg/m^2 and signs of mild dehydration, with normal blood pressure. The patient denied weight loss in the last year.

Further diagnostic workup was performed, showing renal failure (see laboratory values in Table 1), pancytopenia, and an altered liver function. In addition, the patient presented with low albumin, and also low prealbumin, normal corrected calcium, hypophosphatemia, hypomagnesemia, hyperuricemia, hypochloremia, metabolic alkalosis with high bicarbonate, hyponatremia, and hypokalemia. The urinary test revealed an elevated pH, hematuria, urinary proteins of 0.28 g/24 h, urinary albumin of 146 mg/24 h, and hypophosphaturia, with no alterations in the excretion of other electrolytes. Renal ultrasound showed kidneys of normal size, with slightly increased renal cortical echogenicity and no alterations in the urinary tract. Laboratory evaluations showed that IgA was high and complement C3 was low, without other seroimmunological alterations. It was not possible to determine diuretics in urine.

Regarding the finding of renal failure with hematuria, we decided to perform a kidney biopsy. Twenty-three glomeruli were evaluated, of which 3 presented periglomerular fibrosis and the others showed mesangial proliferation and expansion

Table 1 Laboratory parameters of the patient at admission and after the withdrawal of possible external triggers and with the restoration of adequate nutrition

Laboratory parameter	At admission	After the treatment
Leukocytes, mcL	2460	12.050
Hemoglobin, g/dl	7.4	8.8
Platelets, mcL	47,000	397.000
Bilirubin, mg/dl	3.73	0.36
Aspartate transaminase, U/L	262	39
Alanine transaminase, U/L	70	49
Gamma-glutamyl transferase, U/L	516	159
Alkaline phosphatase, U/L	264	87
Albumin, g/dl	2.5	3.5
Prealbumin, mg/dl	15.6	22
Urate, mg/dl	9.5	11.1
Creatinine, mg/dl	9.13	3.3
Phosphate, mg/dl	1.6	3.5
Magnesium, mg/dl	1.3	2
Sodium, mmol/L	127	139
Potassium, mmol/L	2.7	4.5
Chloride, mmol/L	65	97
Blood pH	7.55	7.42
Bicarbonate, mmol/L	56	28.8
IgA, mg/dl	1023	n.a
Complement C3, mg/dl	55.9	107.8
Urinary pH	8.5	n.a
Urinary red blood cells per field	167	n.a
Urinary proteins, g/24 h	0.28	0.44
Urinary albumin, mg/24 h	146	67.1

n.a not available

with Periodic acid–Schiff (PAS-positive) deposits (Fig. 1a). No crescents were observed. The interstitium showed histologic findings of chronicity, with moderate interstitial fibrosis and moderate tubular atrophy. It also highlighted acute tubular necrosis and large calcium phosphate crystals in the tubular lumen and tubular basal membranes (Fig. 1b). Immunofluorescence revealed granular and mesangial deposition of IgA (+++), C3 (++), kappa (++), and lambda (++). So the histologic diagnosis was of IgA nephropathy with an Oxford score of 3/5, along with a calcium phosphate crystalline nephropathy, with moderate signs of associated chronicity.

Regarding pancytopenia, bone marrow biopsy and aspiration (BMBA) were performed. BMBA showed a hypocellular bone marrow with signs of dysmegakaryopoiesis and a focal spindle cell infiltrate with atypical vascular proliferation, without histological or immunophenotypic changes suggestive of myelodysplastic syndromes or leukemia. They concluded that it was a vascular proliferation with the appearance of a benign hemangioma.

Regarding the altered liver function, an ultrasound showed a slightly hyperechoic liver suggesting a nonspecific liver disease. The autoimmune liver tests showed no alterations.

Our patient repeatedly denied drug or toxic abuse and he claimed that he followed a healthy and balanced diet. A few weeks after admission, his family members confessed to a strict restriction of energy intake relative to requirements in our patient, accompanied by episodes of alcohol abuse. We also suspected a possible use of diuretics.

The patient and his family members were questioned in more detail by the psychiatry department. A restriction of daily food intake, inability to gain weight, misuse of diuretics, episodes of binge eating, and moderately severe underweight were discovered. He has diagnosed with moderately severe AN, probably a binge eating/purging type, following the diagnostic criteria of DSM-5 [1]. Also, they indicated an impaired ability to stop or control alcohol use by our patient as being suggestive of an AUD with episodes of binge drinking [3].

After all these findings, our patient was diagnosed with CKD probably secondary to chronic interstitial nephritis due to crystalline nephropathy with calcium phosphate deposition, presumably originating from malnutrition, added to the heavy episodic drinking and the possible use of diuretics concomitantly. Also, he was diagnosed with an IgA nephropathy which could be secondary to nonspecific liver disease in the context of alcoholism and anorexia nervosa. From the hematological perspective, the findings observed in the BMBA indicated the state of malnutrition [7].

The patient was discharged to the psychiatric department, where he was initiated on a supervised oral diet. A hypercaloric and normoproteic diet with a daily intake approximately of 2200 kcal and 66 g of proteins was prescribed. With the restoration of adequate nutrition and the withdrawal of possible external triggers, his liver function tests, pancytopenia, and the electrolyte alterations were normalized (see laboratory values in Table 1). Renin–angiotensin–aldosterone system inhibitors (enalapril 10 mg per day) were initiated on discharge and, when the results of

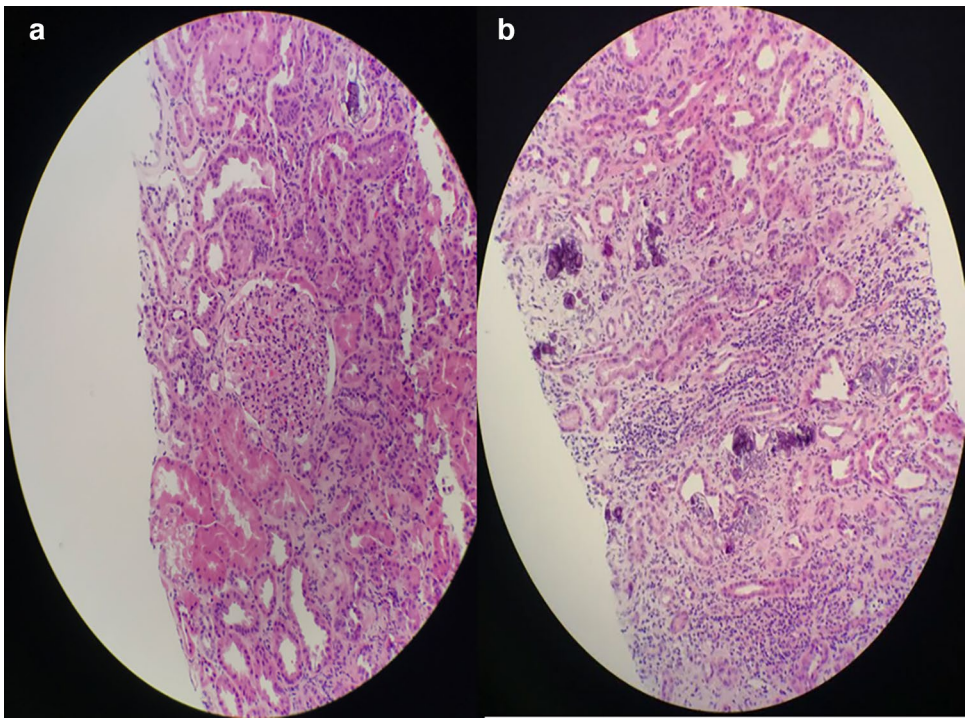

Fig. 1 **a** H-E (X100): Renal glomerulus with mesangial proliferation due to hyaline deposition. **b** H-E (X100): Renal parenchyma with deposits of calcium phosphate crystals at the tubular and interstitial level together with an interstitial inflammatory infiltrate with monocytoid characteristics

the kidney biopsy were revealed, the corticosteroids that have been started empirically at the time of admission were progressively withdrawn from mg/kg/day. The blood pressures presented values of 136/84 on discharge. The pharmacological treatment on discharge also included calcium, omeprazole, and allopurinol. Full recovery of renal function was not achieved, maintaining a creatinine of 3.3 mg/dl and a glomerular filtration rate of 23 ml/min/1.73 m^2, being consistent with the histologic findings of chronicity in the kidney biopsy. The patient also stayed with anemia and hyperuricemia, probably secondary to advanced chronic kidney disease.

Discussion

We report a case of a young male with multi-organ involvement at admission, including pancytopenia, electrolyte alterations, impaired liver function, and renal failure. The kidney biopsy revealed calcium phosphate crystalline nephropathy and IgA nephropathy. Further investigation was performed uncovering a possible masked diagnosis of AUD and AN, which could justify the dysfunctions that our patient presented upon his admission. When we are looking for the cause of an organ failure in a young adult, we usually think of primary or hereditary causes [5]. With the normalization during the admission of the electrolyte alterations, pancytopenia, and liver function, we searched for an external trigger that could explain the multi-organ complications that our patient initially presented.

We observed some findings which may explain the presence of chronic interstitial nephritis due to crystalline nephropathy with calcium phosphate deposition in our patient. On the one hand, AN favors calcium phosphate crystallization through various mechanisms, such as dehydration, hyperuricemia, increased oxidative stress, and hypomagnesemia, among others [8]. The abuse of diuretics, such as furosemide or acetazolamide, which could not be demonstrated in our case, also promotes crystallization by alkalizing the urine, intensifying dehydration and hypomagnesemia, and our patient presented alkaline urine at his admission. On the other hand, alcohol abuse also favors calcium phosphate crystallization by similar mechanisms to anorexia and also promotes hypocitraturia [6].

In our case, the findings of chronic liver disease were probably secondary to AUD and chronic malnutrition as it has been widely reported [9]. Alcohol consumption may promote a broad spectrum of liver disorders, ranging from alcoholic fatty liver to more severe lesions encompassing liver fibrosis or cirrhosis and hepatocellular carcinoma. Alcohol consumption may damage the liver through different mechanisms such as direct hepatotoxicity, reactive oxygen species production by alcohol metabolites, activation of innate immunity, and the production of pro-inflammatory cytokines, among others [9].

The hypocellularity and the gelatinous transformation of the bone marrow observed in our patient have been described in patients with AN, and the reversibility of the pancytopenia of our patient with the restoration of adequate nutrition favors this association. Abella et al. [7] analyzed the BMBA of AN patients and observed that the bone marrow of patients with AN can be normal, hypoplastic or aplastic, with partial, or focal gelatinous degeneration, or with complete gelatinous degeneration. They also correlated these patterns with the amount of weight loss [7]. Gelatinous transformation of bone marrow can be the revealing feature of AN. These potentially reversible associations might prove life threatening if misdiagnosed.

To our knowledge, this is the first case which reports a simultaneous occurrence of AN, AUD, and kidney injury, specifically chronic interstitial nephritis due to crystalline nephropathy with calcium phosphate deposition and IgA nephropathy, also associating hematologic complications and liver disease. In our patient, the kidney biopsy revealed histologic findings of chronicity and the ultrasonography showed an established liver disease. This discovery denotes a repeated and persistent abuse of nutritional and toxic habits mentioned, and also alerts of the lack of total reversibility of the multi-organ involvement in our patient. Therefore, an early detection of these behaviors and these associated mental disorders is very important to allow us to offer appropriate management to these patients.

Conclusions

This case reports severe and probably underdiagnosed complications in the relation of AUD and AN, along with a previously not reported kidney injury. This multi-organ involvement may lose its reversibility if AUD and AN remain persistent. Therefore, early detection and treatment of AUD and AN is mandatory.

What is already known on this subject?

Anorexia nervosa frequently coexists with alcohol use disorder, affecting every organ and increasing mortality. Secondary nephropathies present a low incidence in young adults.

What does this study add?

The coexistence of IgA nephropathy and calcium phosphate crystalline nephropathy has not been previously reported.

This is the first case reporting simultaneous occurrence of anorexia nervosa, alcohol use disorder, and calcium phosphate crystalline nephropathy and IgA nephropathy, associating hematologic and liver diseases.
Our case report also alerts about the lack of reversibility of this multi-organ involvement if alcohol use disorder and anorexia nervosa remain persistent.

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Declarations

Conflict of interest G.M.G.S., A.M.R., X.B.F., N.M.A., M.C.H., B.B., H.I., G.M.E., I.G.M., C.N.P., C.M.C.D., M.P.T., P.T.E., and J.C.M. have no conflicts of interest to declare.

Ethical approval All procedures performed in this case involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Written informed consent was obtained from the patient.

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