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Iatrogenic thyroid dysfunction in peritoneal dialysis

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To the editor: The list of drugs that may cause changes in thyroid hormone levels would be endless (amiodarone, metformin, dopamine, dobutamine, propranolol, carbamazepine, lithium, glucocorticoids….).[1,2] However, radiographic contrast agents[3] and iodine-containing solutions used as general antiseptics and broad-spectrum disinfectants, such as povidone iodine, may also cause thyroid dysfunction.[4] Thus, it is known that povidone iodine contained in the disconnect caps of peritoneal dialysis may be a factor contributing to changes in thyroid function.. The patient population with a higher risk is however limited to infants and children on peritoneal dialysis with small filling volumes, where iodine concentration in the dialysis fluid is higher, while thyroid function changes are considered uncommon in the adult population.[5]

The case of an elderly female patient who showed changes in TSH levels probably induced by the iodine contained in the peritoneal dialysis cap is reported.

This 70-year-old patient had been diagnosed CKD secondary to renal amyloidosis in the setting of a familial amyloidotic polyneuropathy. She also had cardiac amyloid infiltration, and had been implanted a pacemaker in 2005. In addition, the patient had chronic diarrhea due to intestinal infiltration.

Proteinuria was initially found in January 2004, and progressed to levels in the nephrotic range. The patient showed a progressive renal function impairment since April 2005, and was implanted a peritoneal dialysis catheter in February 2006.

Continuous ambulatory peritoneal dialysis was started on 12-04-06, but a catheter leak occurred and a switch to intermittent nocturnal peritoneal dialysis with cycler and low volume (1200 mL per cycle) was made on 28-04-06. The leak subsequently resolved.

The patient had not previously shown any change in thyroid function, and normal TSH levels were found before the start of dialysis. Low, sometimes undetectable TSH levels were seen after the low volume dialysis technique was started. T3 and T4 levels were within the normal range, and anti-thyroid antibodies were normal. The endocrinology department was consulted, and a thyroid ultrasound was performed, showing a diffuse thyroid enlargement that was related to the underlying disease. Fine needle puncture allowed for ruling out malignancy or an amyloid infiltrate. While uncommonly, infiltrative diseases such as amyloidosis may also cause thyroid dysfunction.[6]

The patient was asymptomatic at all times and did not require additional treatment. Once the catheter leak was resolved, filling volume could be increased, but continues to be low (1500 mL), now because of the discomfort experienced by the patient with higher volumes. Hormonal changes persist.

Similar to when treatment is started with drugs altering thyroid function, thyroid hormone monitoring is also recommended in patient on peritoneal dialysis with small filling volumes, because the iodine contained in the disconnect cap may reach high concentrations in peritoneal fluid and pass into the blood, inducing iatrogenic changes such as those occurring in the rare case reported.

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Primary antiphospholipid syndrome: dormant, not cured

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To the editor: A case that may be of clear practical help for healthcare professionals treating similar patients because of some characteristics of its clinical course, response to treatment, and potential confusion for responsible physicians is reported below.

Case report: A 24-year-old female patient who experienced generalized tonic-clonic seizures when she was 20. Physical examination revealed postictal disorientation, mild Raynaud's phenomenon, and malar erythema. She had severe autoimmune hemolytic anemia due to complement-fixing hot IgG antibodies and thrombocytopenia; renal failure with serum Cr levels of 2.2 mg/dL and dysmorphic RBCs; hypocomplementemia (C3 80 mg/dL, C4 8 mg/dL), ANA 1/640, IgG anticardiolipin 57.7 UGP/mL (negative < 10), IgM anticardiolipin 58.2 UGP/mL, lupus anticoagulant DVV test 131 (negative < 45). MRI of the brain showed cortical-subcortical vasculitic-ischemic

lesions. The only remarkable data in the patient history was that she smoked 20 cigarettes daily.

Based on diagnosis of a primary antiphospholipid syndrome (PAPS) and because of persistent severe hemolysis and renal function impairment, plasmapheresis (4 sessions on alternate days) was started, but no improvement was obtained in thrombocytopenia, serum creatinine, or anticardiolipin levels. Mycophenolate mofetil 500 mg/12 h and methylprednisolone 120 mg/day were started. Due to lack of response to this second treatment, mycophenolate was replaced by cyclophosphamide as an IV bolus (750 mg/day, 4 doses) and acetyl salicylic acid 100 mg/day. ACEIs were also added. Due to persistent severe hemolytic anemia and poor kidney function after the first cyclophosphamide cycle, it was decided to use as adjuvant the chimeric anti-CD2 antibody, rituximab (Mabthera, Roche, two 1 g doses). At the end of rituximab treatment, hemolytic anemia had disappeared, and a renal biopsy could be performed, showing a pattern of occlusive arteriolar disease consistent with clinical diagnosis.

Complement and anticardiolipin antibody levels normalized and renal function improved, with serum creatinine of 1 mg/dL and creatinine clearance ranging from 80 and 100 mL/min after 3 and a half years of follow-up. BP was maintained between 80 and 100 mmHg with ACEIs and ARBs. In a new MRI of the brain, lesions detected in 2003 had disappeared. Anticoagulation with Sintrom to maintain INR between 2 and 2.5 was administered as maintenance treatment. Immunological parameters remained negative in successive, frequent measurements. After completing 4 years of anticoagulation and because of the total absence of immunological activity, discontinuation of anticoagulation was considered, since PAPS was in complete remission. The need for antihypertensives was independent from this remission, considering the type of arteriolar lesions found in the biopsy.

In December 2007, the patient experienced infection by type 1 human papilloma virus, that caused lesions consistent with a high-grade squamous intraepithelial lesion (HGSIL). Lupus anticoagulant was negative, and C3 and C4 levels were normal. Antinuclear antibodies at a titer of 1/320 were only detected. A gynecological procedure for taking deep histological samples was decided, for which Sintrom was replaced by enoxaparin at prophylactic doses (40 mg/day). On the fourth day of treatment, the patient reported blurred vision in her right eye, that gradually increased in the 3 following days. An eye fundus examination revealed amaurosis in the right eye due to complete thrombosis of the central retinal vein, with abundant retinal bleeding.

Diagnostic criteria for PAPS were established in the Sapporo Conference in 1999 and revised in Sydney in 2005, and classified catastrophic PAPS as a separate group.[1]

Though the pathogenetic mechanisms of the disease are now better understood,[2] its treatment is only based on prevention and treatment of arterial and venous thrombosis, and there are hardly any data about measures directed to pathogenetic factors.[3] Thrombosis is the most easily recognized sign of PAPS, and may depend on endothelial activation. This would involve local stimulation of adhesion molecules and procoagulant proteins, which would in term induce thrombus formation. However, other manifestations of the disease, such as livedo reticularis, cardiac valve disease, thrombotic microangiopathy, hyperintense lesions in MRI, or repeated fetal loss cannot be explained by this mechanism.

Risk of recurrent thrombosis in these patients is high, up to more than 50% per year depending on the series.[4] In long-term treatments, it is not completely clear whether oral anticoagulation at doses to maintain an INR > 3 is more effective that anticoagulation to achieve an INR of 2-3. Lifetime anticoagulation is currently advocated in patients who have experienced any thrombotic event.[5] In view of such a favorable course and total negativization of immunological markers, the possibility of discontinuing or decreasing the dose of permanent anticoagulation was considered.

Since a treatment with a real chance of destroying the clone producing harmful antibodies had been administered, a possible cure was a logical consideration. There are not, however, epidemiological criteria or data allowing to establish whether PAPS may be cured.

However, the disease itself dispelled this doubt: the occurrence of a retinal venous thrombosis when anticoagulation was decreased showed the existence of clinical activity.

Use of combined chemotherapy may provide a long-term solution for an extremely severe disease such as PAPS. In this case, complete immunosuppression, associated to rituximab, was used as background treatment. There are very few reports in the literature on the use of these drugs in PAPS. Mycophenolate[6] and rituximab[7] have only been used for PAPS with hemolytic anemia refractory to standard treatment with high-dose corticosteroids. Use of cyclophosphamide for this condition has not been reported.

It should be noted that articles published report improvement in hemolytic anemia, but do not provide information about what happened to the other components of PAPS, such as renal involvement and cerebral lesion. This case again illustrates the possibility of inducing a prolonged inactivity of the disease by using first-line immunosuppressive treatment. It should also be emphasized that, as occurred in this case, the greatest value of rituximab is that it causes a rapid decrease of antibodies with a high pathogenetic capacity, such as those inducing hemolytic anemia, present in this patient in clinically and analytically high levels.

As a general rule, in the larger series systemic lupus erythematosus (SLE) was not developed by more than 80% of patients with PAPS: However, it should be noted that the onset of the clinical picture of autoimmune hemolytic anemia and hypocomplementemia would define a subgroup of patients with a significant risk of subsequent occurrence of SLE.[8]

Other factors associated to late occurrence of SLE include the presence of a Raynaud's phenomenon, migraine, psychiatric changes, and syndromes such as multiple sclerosis.[9,10] While this patient had several of these signs, persistent negative results in immunological tests for SLE supported the possibility of a complete remission/cure. However, clinical facts proved the opposite. A history of retinal venous thrombosis in PAPS is rare, and is usually found in patients with antiphospholipid antibody activity.[11,12] The reported patient had no such activity, but the fact that certain immunological positivity was found, e.g. antinuclear antibodies, allows for speculating about the existence of some active procoagulant mechanism.

Based on the foregoing, it may be stated that while no evidence from a sufficient number of cases is available to support use of more intensive immunosuppressive therapy in these patients, such treatment may provide long-term or indefinite disease-free periods in these patients. However, despite the risk involved in permanent anticoagulation, this case is a particularly clear example of risk persistence in spite of a prolonged immunological inactivity.

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Sclerosing peritonits with a predominant inflammatory component after fungal peritonitis

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To the editor: Cases of fulminant sclerosing peritonitis (SP) following acute peritonitis with a dramatic response to steroids have recently been reported.[1,2] A case of fulminant SP occurring after fungal peritonitis is reported below.

A 87-year-old female patient on CAPD had experienced three episodes of peritonitis over the previous 5 years. The last episode was caused by coagulase-negative staphylococci. On the second week of treatment, after an initial good response, the patient experienced severe abdominal pain, with fever and a turbid fluid. *Candida albicans* grew in peritoneal fluid cultures, and the patient was therefore administered fluconazole and removed the peritoneal catheter, which resulted in immediate clinical improvement. On the fifth day, the patient had severe abdominal pain, fever of 38 ºC, leukocytosis with increasing neutrophilia, a shift to the left, and a significant increase in C-reactive protein levels (CRP). Repeated blood cultures were negative, and fluconazole-sensitive *C. albicans* was detected. A CT scan of the abdomen revealed ascites, peritoneal thickening with increased vascularization, and doubtful loop centralization. Steroids (1 mg/kg/day) and tamoxifen (20 mg/day) were started. Abdominal pain and fever disappeared and CRP levels decreased in 48 hours (fig. 1). Steroid treatment was maintained for six months, and the asymptomatic patient continues on tamoxifen with a trend to a decreased dosage (nine months in total).

The most typical presentation of SP is intestinal obstruction. The more insidious form may show ultrafiltration failure (in HD patients), nausea, vomiting, anorexia, weight loss, and abdominal pain. Initial radiographic findings are non-specific, and signs of intestinal obstruction later occur. The condition is documented by laparotomy or laparoscopy.

Some case reported of SP starting early after severe peritonitis ran a fulminant course, with a great inflammatory component and a good response to steroids (fulminant SP).[3] Diagnosis is made by exclusion and requires a high grade of suspicion. It could correspond to the pre-encapsulating phase described by Nakamoto, in which steroids may act as an acute treatment for the peritoneal inflammatory phase and association of tamoxifen may probably prevent development of fibrosis. The favorable response of our patient to steroids probably confirms the existence of an inflammatory reaction, and the subsequent clinical and radiographic course may be