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Pleuro-pericarditis Revealing Celiac Disease

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Abstract Background: Celiac disease (CD) is an auto immune disease that often one or more disorders may be associated especially endocrine but also heart disorders. We report a patient case with idiopathic hypo-parathyroidism and CD revealed by pleuro-pericarditis. Observation: A 23-year-old woman was admitted in intensive care unit for epileptic-evil condition following dyspneising pleurisy. She has been diagnosed as epileptic case since 5 years and she had undergone surgery for right cataract. On the physical examination, she exhibited a tachycardia and breathing rales at pulmonary auscultation. She had clinical signs of chronic hypocalcaemia, without gastrointestinal complaints. Chest x-ray revealed cardiomegaly and right pleurisy. The cardiac ultrasound demonstrated very abundant bilateral pleural and pericardial effusion. The phosphocalcic balance resulted in a severe hypocalcemia at 0.8 mmol / l and hypo-parathyroidism was confirmed. In addition to the surgical drainage, she had calcium and vitamin D supplementation. CD was suspected after the resistance for a high supplementation and confirmed by endoscopy. Under a gluten-free diet (GFD), the evolution was marked by the stability of serum calcium levels and disappearance of pleural and pericardial effusion. Conclusion: The possibility of celiac disease should be considered in patients with hypoparathyroidism and pericarditis that seems unduly difficult to treat. This should be evaluated even in the absence of gastrointestinal symptoms.

Keywords: *hypocalcoemia, malabsorption syndrome, pleuro-pericarditis, hypoparathyroidism, celiac disease*

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1. Introduction

Celiac disease (CD) is an auto immune small intestinal mucosal disorder that occurs in genetically predisposed individuals as the result of an immune response to gluten. It is present in approximately 1% of the population [1]. Diarrhea has become a less common mode of presentation (<50% of cases) than it once was [2]. During the last decades CD has increasingly become recognized as a multi-organ disorder, and has been linked to a number of complications including malignancy [3], autoimmune disorders [4,5] and tuberculosis [6]. Individuals with CD are also at increased risk of death from ischemic heart disease [7]. To our knowledge, research on CD and pericarditis is limited to case-reports [8,9,10,11,12].

We report the clinical case of an association between idiopathic hypoparathyroidism (IH) and a celiac disease revealed by pleuro-pericarditis.

2. Case Report

A 23-year-old woman with a history of epilepsy for 5 years and cataract of the right eye operated 3 years ago, admitted in intensive care unit for epileptic-evil condition. The clinical examination found a tachycardia at 104 beats/min, a blood pressure at 10/4cmHg. Endocrinological examination was normal. The inflammatory assessment revealed hyper-leucocytosis at 22,700 mmol/l. Chest x-ray revealed cardiomegaly and right pleurisy. The electro-cardiogram found diffuse microvoltage and flattening T-wave. A cardiac ultrasound demonstrating a bilateral pleural effusion and abundant pericardial with signs of pre-tamponade. The patient had pericardial and pleural surgical drainage. Bacteriological, mycological, immunological and tuberculosis investigations were negative. The patient was treated by colchicine 1 mg/day and aspegic 100 mg / day. The cardiac echocardiography realized at 1 week after surgery demonstrated a very low abundance pleural and pericardial effusion.

On physical examination, we noticed chronic hypocalcaemia clinical signs (muscle cramps, cataract of the right eye). The biological analysis showed a severe hypocalcemia (0.8 mmol / l). The parathyroid hormone was less than 3 pg / ml which allowed to retain the diagnosis hypo-parathyroidism.

There was no improvement in serum calcium levels after oral calcium and vitamin D (calciferol) supplementation on reversal of calcium parenteral supplementation (Figure 2). Thus celiac disease has been suspected. The patient had no chronic diarrhea but biological malabsorption signs (hypo-calcemia, anemia, hypo-albuminemia and hypocholesterolemia). Anti-transglutaminase antibodies were positive. Oeso-gastroduodenal fibroscopy confirmed villous atrophy. The patient followed a Gluten Free Diet

(GFD) and had an oral calcium and vitamin D supplementation. The evolution was marked by an improvement in the biological malabsorption signs: disappearance of anemia, rise in blood protein and calcium levels (Figure 1) and disappearance of pleural and pericardial effusion (Figure 2a and Figure 2b).

3. Discussion

During the last decades CD has increasingly become recognized as a multi-organ disorder including autoimmune disorders [4,5] and cardiovascular diseases [11].

Several study showed that patients with CD are also at increased risk of ischemic heart disease [13], atrial fibrillation [14], cardiovascular death [15], dilated cardiomyopathy [16], autoimmune myocarditis and pericarditis [7,17]. All these studies were however, based on few positive events and with the exception of the prospective Danish study [18], they were cross-sectional and did not take into account whether CD preceded or ensued heart disease [19]. However, research on CD and pericarditis is limited to case-reports [8,9,10,11,12].

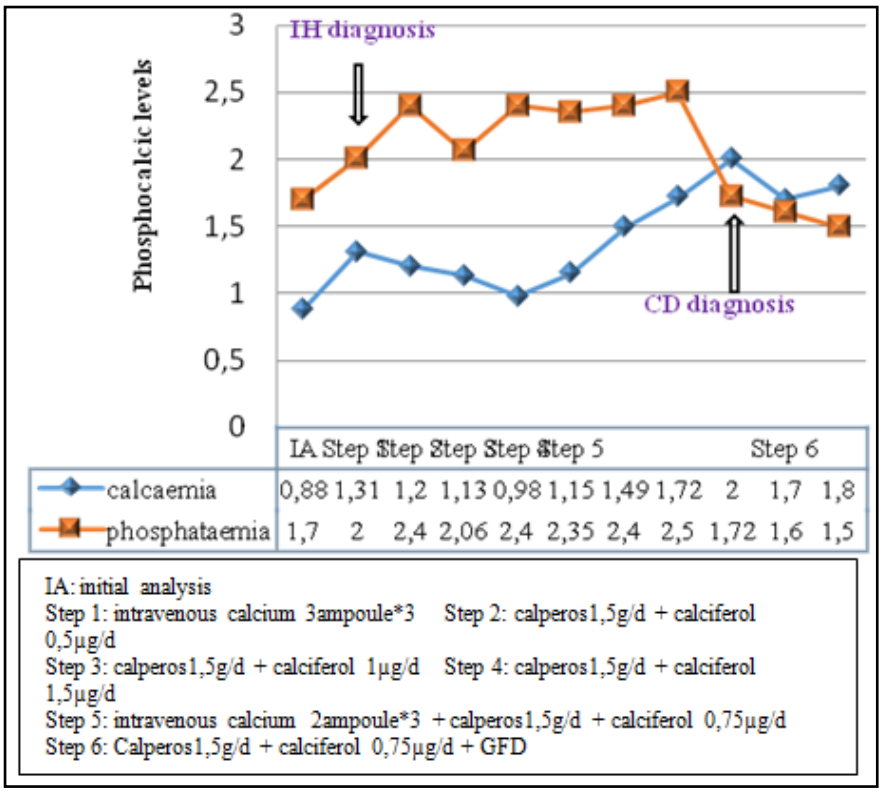

Figure 1. Evolution of calcium and phosphoric levels under treatment

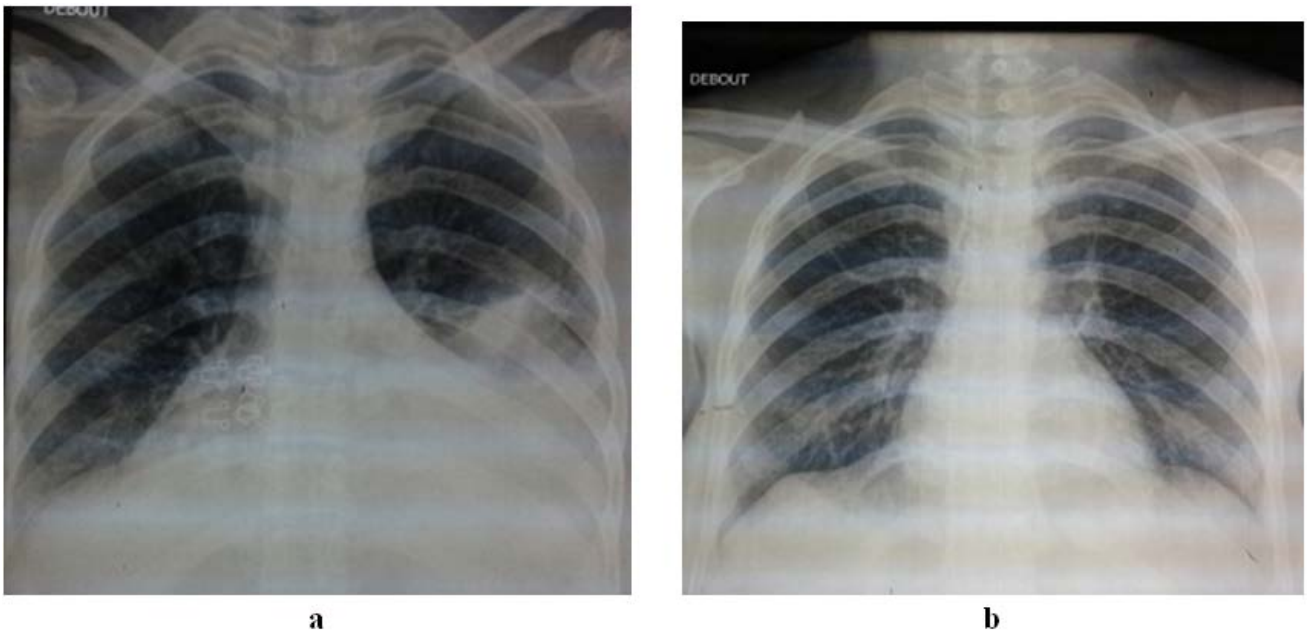

Figure 2. a: Chest x- ray before GFD: Pleuro-pericarditis, **b:** Chest x ray after GFD: disappearance of Pleuro-pericarditis

The majority of cases of pericarditis are idiopathic [20]. A viral etiology is often implicated but rarely proven [20]. In some cases of pericarditis, particularly when recurrent, autoimmune or hypersensitivity states have been implicated. This may be relevant to celiac disease where an association with immune disturbance is recognized [20].

In this context, pericarditis has previously been reported in CD, and it may even manifest as a primary presenting feature [21]. The likely mechanism is a disturbed humoral and cell-mediated immunity including other autoimmune reactions. There is deposition of circulating immune complexes originating from the small intestine, which may resemble the etiology of pericarditis similar to the one encountered in serum sickness [12,21]. The mechanisms are likely related to pericardial deposition of soluble antigen-antibody complexes when there is excess of antigen [20,21].

However, in the cohort study conducted by Elfström et al, they found no statistically significant association between CD and having later cardiomyopathy, pericarditis or myocarditis, but the risk estimated for pericarditis in CD were statistically significantly higher in CD diagnosed in adulthood compared with CD diagnosed in childhood [19].

Riccabona in his study reported that 50% of children with celiac disease had asymptomatic and limited pericardial effusion that only detectable with instrument [22]. Anemia is the most common presentation of CD in adults and it may be the only presentation of disease and iron deficiency is the major cause of this anemia [23]. Anemia and leg edema were the major findings and pericardial effusion was asymptomatic in the case reported by Farzaneh [11]. In our patient, anemia was not severe, pericardial effusion was not symptomatic and it was an incidental finding; and the diagnosis of CD was based on serologic and histologic findings.

After appropriately excluding other autoimmune conditions and if pericardial symptoms of CD patients do not completely respond to GFD alone, several authors recommended steroids as a first-line therapy at least for a while [20,24]. It is in contrast to the treatment of acute idiopathic pericarditis where one would consider either non-steroidal anti-inflammatory drugs or colchicine [21,24]. Colchicine has not been extensively studied in patients with autoimmune diseases; however at least 7% of the patients in CORP-2 trial had underlying autoimmune conditions and benefited from the use of colchicine [25]. Our patient had a pericardial surgical drainage followed by treatment with colchicine and aspegic and she followed a GFD.

However, the intestine is one of the most involved organs in adverse drug reactions (20 – 40%) [26]. The entero-toxicity may be an immediate but also delayed effect. Colchicine can essentially lead to diarrhea. Isolated cases of villous atrophy were attributed to mefenamic acid, azathioprine, methotrexate, ticlopidine and recently to mycophenolate and olmesartan [27]. This can't be the case for our patient. The fact that the patient didn't take anti-inflammatory drugs nor colchicine before and the positivity of anti-transglutaminase antibodies and the favorable clinical evolution under GFD are against the diagnosis of drug enteropathy.

On the other hand, IH can be associated with other digestive autoimmune diseases that may cause diarrhea [28]. Cases of IH coexisting with CD are described in a handful of cases in the literature, [29,30] although this situation occurs very rarely and mainly in patients with long standing disease and therefore lengthy exposure to antibodies [31]. The described association could be an occasional finding, but a common pathogenesis of both diseases can be hypothesized on immunological basis [30]. Studies have found that parathyroid antibodies can be of two types: one specific for the parathyroid gland, the other non- specific and able to mimic the anti-endomysial antibodies associated with CD. Besides, tissue transglutaminase antibodies produced in CD have been shown to cross-react with other antigens and endomysial antibody reactions on parathyroid tissue have been shown to lead to parathyroid atrophy [31,32,33]. Soma et al. assessed in their comparative cohort study that the prevalence of CD and anti- tissue transglutaminase autoantibodies (anti-tTGAbs) in IH was 6,4% [34]. The age of the disease onset ranged from early childhood to old age [30].

Hypoparathyroidism is a chronic disorder characterized by hypocalcaemia, tetany, cataract, basal ganglia calcification and convulsions [35,36]. Our patient was 23 years old and she had probably chronic hypocalcaemia that can be involved in recurrent cataract and in the epilepsy.

In some reports, hypoparathyroidism was diagnosed some years prior to the diagnosis of CD [30], while in other reports, the diagnosis of hypoparathyroidism was made concomitantly with the diagnosis of CD [37]; such as in our case report.

Hypoparathyroidism causes hypocalcaemia through a fall in parathyroid hormone levels, leading to reductions in bone reabsorption and intestinal calcium absorption and, in patients without end-stage renal disease, increased calcium excretion. In CD, the mechanism leading to hypocalcaemia is chronic inflammation of the intestinal mucosa leading to malabsorption of vitamin D and calcium [38]. Hypocalcaemia is often exacerbated by a decreased intake of dairy products because of lactose intolerance, as lactase cannot be produced by degenerated intestinal epithelial cells and is not available to cleave the lactose in dairy products [39].

Hypocalcaemia may present as an asymptomatic laboratory finding or as a severe, life-threatening condition. Upon the diagnosis of acute hypocalcaemia, a rapid treatment regimen may be necessary. In contrast, chronic hypocalcaemia may be well tolerated by the patient with hypoparathyroidism like the case of our patient, but treatment nonetheless remains necessary in order to prevent long-term complications [37].

If suspected by resistance to vitamin D supplementation [40], the coexistence of CD must be ruled out by duodenal biopsy. In such cases, GFD should be included in the treatment regimen [30,41]. Once a GFD is adhered to, approximately 70% of patients notice symptomatic improvement within two weeks, anti-endomysial antibodies generally disappear in 6–12 months and plasma calcium levels normalize quickly [42], as illustrated also in our case report.

Many other studies also assessed the effect of a GFD on calcemic control in patients with IH, found to have CD. A GFD led to improvement in weight and calcium control during follow-up in patients with hypoparathyroidism and CD [34,37,41,43]. In fact, in some cases, hypercalcemia was noted after the institution of a GFD, necessitating a reduction in the daily dose of calcium and vitamin D therapy [42].

However, despite dietary compliance, the speed and degree of histologic improvement is unpredictable but invariably lags behind the clinical response [42]. Data indicates that mucosal inflammation may persist for many years and histologic improvement may not be evident on repeated biopsy for 2–3 months [42].

4. Conclusion

Our observation is particular by the simultaneous diagnosis of hypoparathyroidism and CD following severe pleuro-pericarditis.

The possibility of CD should be considered in patients with hypoparathyroidism that seems unduly difficult to treat. This should be evaluated even in the absence of gastrointestinal symptoms.

So it is important to be aware of a potential co-occurrence of CD in patients with IH, wherein a GFD has beneficial impact on calcium control.

Besides, in such association, a long-term monitoring is necessary to detect recurrence of pericarditis.

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