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Atypical, Delayed Presentation of Asymptomatic Celiac Disease; Case Report and Review of Literature.

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ABSTRACT

Objectives: To describe the association and relationship of the clinical manifestations and the metabolic changes in a case of asymptomatic Celiac Disease (CD), Primary Hyperparathyroidism (PHPT) and Plummer-Vinson Syndrome (PVS).

Methodology: A case report presenting a 37-year old female, with a 3 - year progressive lower back pain (LBP), fatigue and history of anaemia, and referred to Rafidia medical centre. No suggestive symptoms of malabsorptive disease were observed. Detailed clinical assessment revealed proximal myopathy, sever osteoporosis, normal calcium and phosphorus, elevated alkaline phosphatase and parathyroid hormone level.

Results: Left parathyroidectomy was done, followed by sever hypocalcemia non-responding to oral calcium. Serological and endoscopic screening for Celiac Disease was positive and associated with oesophageal web. Treatment with gluten-free diet (GFD), oral calcium and oral iron yielded remarkable clinical biochemical and radiological improvement.

Conclusion: Celiac Disease is asymptomatic for long time, and forms the underlying cause of osteoporoses and anaemia. The associated Primary Hyperparathyroidism makes osteoporosis more sever. Plummer-Vinson syndrome is frequently associated with celiac disease.

Key words: Celiac Disease – Hyperparathyroidism – Osteoporosis - Plummer-Vinson Syndrome.

INTRODUCTION

CD is an autoimmune inflammatory disease of the small intestine in genetically susceptible individuals due to lifelong sensitivity to gluten (a cereal protein present in grain from wheat, barley and rye). It is characterized by mucosal inflammation and villous atrophy of small bowel which lead to symptoms of malabsorption[4-7.] This disease is diagnosed by intestinal biopsy[1.] It is considerably prevalent in the western society; (1%) in both Western Europe and US[2]. The introduction of new serological tests for CD has dramatically increased the chances of its diagnosis, resulting in considerable changes in the clinical prospective of this disease especially the diagnosis of atypical cases[1,4-7]. However, the major problems are found in CD diagnoses: the multifaceted clinical picture and asymptomatic presentation[4,6,8]. *Table 1* shows the typical, atypical and commonly associated conditions of CD[1,3,6]. It is important to highlight that CD is strongly related to some GI malignancies, especially intestinal lymphoma; and it reduces the risk of breast cancer[21].The only treatment of CD is the lifelong gluten-free-diet, with adjuvant proper nutritional consultation that prevents any diet related malnutrition[1,4,6,9].

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Table 1: Typical, atypical and commonly associated conditions of CD

Typical	Atypical	Commonly Associated Conditions
Diarrhea	Abdominal Discomfort	Insulin Dependent D.M
Vomiting	Loose Stools	Autoimmune
Abdominal distension	Flatulence	Thyroididtis
Dermatitis herptiformis[(a)]	Weight Loss	Rheumatoid Arthritis
Recurrent miscarriage	Fatigue	Sjogren Syndrome
	Constipation	Plummer-Vinson
	Iron Deficiency Anemia	Syndrome
	Arthritis	Thyroididtis
	Short Stature	Iga Deficiency
	Osteoporosis	Primary Biliary Cirrhosis
	Oral Mucosal Lesions	Hyperparathyroidsm
	Neurological Symptoms[(B)]	Down's Syndrome
	Psychiatric Symptoms[(C)]	T-Cell Lymphoma
	Pericarditis	

[a] Dermatitis herpetiformis: its skin disorder characterized by itchy, blistering rash appearing predominantly at the knees, elbows and buttocks.
[b] Neurological symptoms: epilepsy, cerebral calcifications, cerebellar ataxia, chronic neuropathies, myoclonic ataxia and dementia.
[c] Psychiatric symptoms: depression, anxiety and behavioural changes.

Primary Hyperparathyroidism (PHPT)

Parathyroid Hormone (PTH) secretion is stimulated by a fall in the extracellular calcium concentration. This stimulates the hydroxylation of 25-hydroxy vitamin D at the proximal convoluted tubule in the kidney, and increases bone resorption through stimulation of osteoclast-activating factors such as interlukin-6 from osteoblasts to restore any tendency to hypocalcemia [14]. PTH does not directly affect gastrointestinal absorption of calcium. The PHT effects are mediated indirectly through regulation of syntheses of 1,25 $(OH)_2D_3$ in the kidney[15]. PHPT has an incidence of 0.1-0.5% in general population, affecting up to 2% of the elderly, with higher incidence in postmenopausal women[10]. PHPT manifestations may range from ostitis fibrosa cytica and renal stones to non specific symptoms[12,10,13]. Summary of symptoms of hyperparathyroidism is shown in (*Table 2*). Monoclonality occurs in parathyroid adenomas, and can be found in sporadic multi gland hyperplasia and familial multiple endocrine neoplasia (MEN) Type I[15].

There is evidence of elevated bone turnover markers and increased risk of fracture in asymptomatic patients with PHPT[12]. Surgery is the only curative treatment for PHPT, with >95% cure rate and complication rate of <5% [1].

Secondary Osteoporosis

Secondary Osteoporosis is defined as osteoporosis in which there is an important identifiable causal factor other than menopause and aging[16]. There is a strong association between celiac disease and osteoporosis because osteoporosis is present in 26-34% of CD patients. This association is caused by malabsorption of calcium, vitamin D and other micronutrients[4]. Secondary hyperparathyroidism can occur in many older individual, and it is aggravated by some disorders that cause secondary osteoporosis especially malabsorption syndromes[16]. High parathyroid hormone is associated with low BMD in untreated celiac patients[17].

Table 2: Symptoms of Hyperparathyroidism

System involved	Main symptoms
Cardiovascular	Hypertension
GIT	Nausea
	Vomiting
	Anorexia
	Constipation
	Abdominal pain
	Pancreatitis
Renal	Nephrocalcinosis
	Nephrolithiasis
	Calciuria
	Polyuria
	Overflow incontinence
Psychiatric	Depression
	Anxiety
	Psychosis
Skeletal	Ostitis fibrosa cystic
	Osteoporosis/osteopenia
	Bone pain
	Pathological fractures
Neuromuscular	Fatigue
	Mayalgias
	Muscle weakness

Plummer-Vinson Syndrome (PVS)

PVS is also known as *Paterson-Brown Kelly Syndrome*, or *Paterson-Kelly Syndrome*. It is a rare syndrome with unknown aetiology, defined by the classic triad of dysphagia, iron deficiency anaemia and oesophageal web[7,18]. Celiac Disease is the most frequent associated disorder[7,18]. Iron deficiency, malnutrition, genetic predisposition, autoimmune processes are among the proposed risk factors of PVS[18]. PVS is related to malignancy of the upper gastrointestinal tract, mainly squamous cell carcinoma of the pharynx[18]. 3 to 15 per cent of the patients with PVS, mostly women between 15 and 50 years of age, have been reported to develop oesophageal or pharyngeal cancer. The prognosis of Dysphagia and anaemia is excellent provided that it is not associated with carcinoma[19].

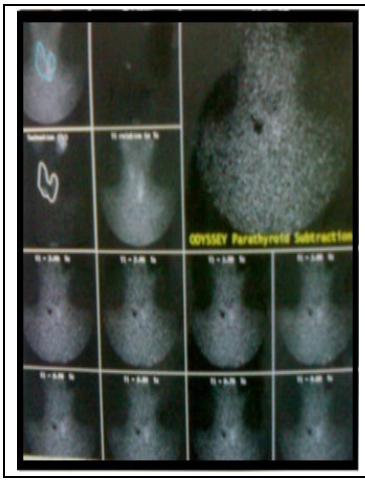
CASE REPORT

A 37-year old female presented with progressive sever pain in her lower back with easy fatigability for the last 3 years. History review revealed documented chronic iron deficiency anaemia of unknown cause since teenage. She used to be on oral iron supplementation but still anaemic. Also, she gave history of recurrent hypocalcemia, where calcium supplementation was given. She denied previous fractures. During the last three years, she was treated for osteoporosis and lumber disc prolapse without showing any improvement.

Multidisciplinary team was involved in the management plan. Initial laboratory data including iron deficiency anaemia, mild hypocalcemia, ESR 33 and hyperparathyroidism, PTH 1350 pg/L (15-65 pg/L) were collected. Thallium Technetium subtraction scan of the parathyroid revealed abnormal uptake of the left side, indicating parathyroid adenoma (*Figure 1*). Parathyroid adenoma was surgically removed; it measured 15x20x25 mm adenoma of the left parathyroid gland (*Figure 2*). The size of the other three glands was normal. Till this moment Celiac Disease was not

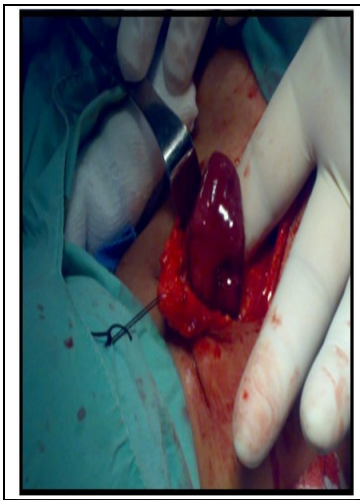
considered. One day after surgery, the patient developed persistent hypocacemia even with maximum doses of parentral and oral calcium and vitamin D. At this stage only, a malabsorption disease was suspected to explain calcium malabsorption. Screening for Celiac Disease showed the followings: elevated alkaline phosphates (ALP) 421 IU/L (20-140 IU/L); 24-hour urine calcium 3.76 mmol/day (2.5-8 mmol/day); 25-hydroxyvitamin D <10 nmol/L (22-116); LDH 748 U/L (80-480 U/L); and positive *Antiendomysial* and *Antitransglutaminase* antibodies.

Figure 1: Thallium Technetium subtraction scan of the parathyroid



Thallium Technetium subtraction scan of the parathyroid evidence of abnormal uptake of the left side, suggestive of parathyroid adenoma.

Figure 2: Adenoma of the left parathyroid gland



1.5X2X2.5 cm adenoma of the left parathyroid gland.

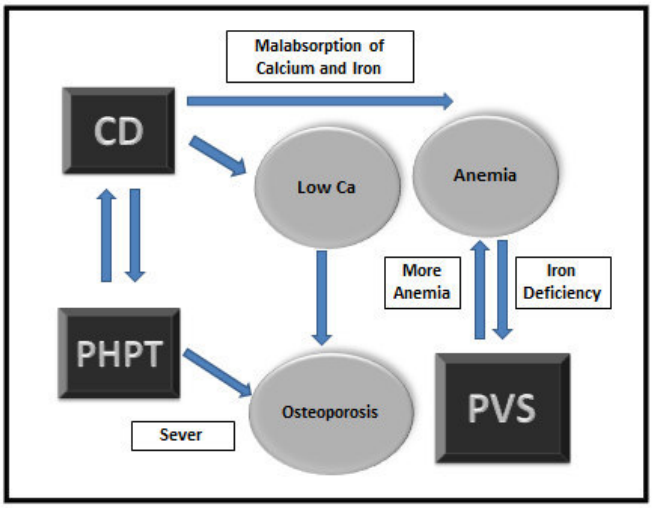
Oesophageal-gastro-Duodeno-scope (OGDS) was indicated to confirm the diagnosis of (PVS) disease. In view of anemia and weight loss. The biopsy showed villous atrophy of different degree, crypt hyperplasia, and esophageal web. Muscle biopsy showed mild nonspecific myopathic changes. MRI of Lumbar spine showed no disc prolapsed. Radiology and bone densmetric was done for different parts of the body showed sever osteoporosis and some scattered cystic changes. Having established the CD diagnosis, detailed consultation regarding strict gluten-free-diet was given by trained dietician; and oral supplementation of calcium, vitamin D and iron were given to the patients prior home discharge. In one year follow up, the patient was markedly improved, returned to normal activity, and gained about 4 kg body weight; but she was still shorter than before. In addition, serum calcium and PTH was normal; and anaemia improved. Bone densimetric tests showed more than 60% improvement compared to that taken upon diagnosis.

DISCUSSION

The patient was presented with LBP, fatigue, anaemia, slightly elevated calcium, normal phosphorus, low vitamin D, sever osteoporosis and very high PTH due to parathyroid adenoma. After parathyroidectomy, the patient developed hypocalcemia that did not respond to the maximal dose of oral calcium which, in turn, led to suspected Malabsorption. The final diagnosis was CD associated with PVS.

The diagrammatic explanation of diseases sequence and their relationships is shown (*Figure 3).* The patient's medical history reported hypocalcemia and iron deficiency anemia at age of 11-25 years which suggested that she had CD and PVS at that time. This deficiency was still relatively tolerable till she gave birth to 5 children, when the requirement of calcium and iron highly increased. As she could not absorb calcium, body responded by bone resorption to correct hypocalcemia, leading to osteoporosis[16]. Hyperparathyroidism was primary because of

Figure 3: Sequence of diseases progression and relation between them



relatively normal calcium, single adenoma and absence of hyperplasia in the other glands. Moreover, reduced expression of Calcium-Sensing receptor protein, which is usually occurs in parathyroid adenoma, was associated with CD; this confirmed the sporadic occurrence of both diseases (CD and PHPT)[20]. Such association resulted in sever osteoporosis to the patient indicated by BMD and elevated ALP due to high rate of bone turnover[12]. The post-operative hypocalcemia happened due to the absence of the effect of PTH on bones. So, shifting of serum calcium to bone accelerated, without replacement from the oral supplementation, a condition known as *Bone Hunger Syndrome*[22]. Depressive symptoms were observed resulting from the impact of the initial diagnosis and chronic pain[3]. Anaemia was explained by both iron deficiency due to malabsorption in CD, and as the most frequent triad of the PVS syndrome[18].

CD is commonly overlooked due to failure of clinicians to consider it in the initial differential diagnosis as CD presents with non-classical symptoms. Many patients are diagnosed with CD when they only have complications, like osteoporosis and malignancies[3]. Hence, the late diagnosis of CD in most cases is due to late referral to hospitals or specialists from the primary care physicians[3], as happened to this case. The association of PHPT with CD has both diagnostic and therapeutic implication[2]. Meanwhile, among CD patients, women have got higher percentage than men (3:2 respectively). This could be because women seek health advice during the reproductive age due to the increase in nutritional requirements[3]. The current case report highlights the importance of early diagnosing of CD, which was missed in this patient; and therefore requires a strong suspicion from the primary care setting, including the involvement of the multi-disciplinary team, before the patient developed complications.

CONCLUSIONS

CD and PHPT share a subtle mode of presentation with many overlapping, nonspecific symptoms that may compound the clinical diagnosis[2]. It is important to look for intestinal malabsorption, especially CD, in patients with normocalcemic hyperparathyroidism[2], unexplained iron deficiency anemia (IDA)[3] and secondary osteoporosis[16]. Early diagnosis of CD and subsequently induction of gluten free diet is the most important factor in preventing CD complications[1,3]. Calcium and bone metabolism disorders are the most frequent complications (26-34%)[3,4]. Plummer-Vinson Syndrome and PHPT are usually associated with CD. Secondary causes of osteoporosis are frequently missed even at specialized clinics. It's recommended to screen CD in all pre-menopausal osteoporotic women without obvious cause of osteoporosis.

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