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CASE REPORT

Adult-Onset Atypical Coeliac Disease Presenting with Severe Anaemia and Hidradenitis Suppurativa: A Case Report

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Abstract

Background: Coeliac disease is an autoimmune disease causing intestinal mucosal damage in response to dietary gluten resulting in malabsorption. It is a rarity in Sri Lanka and southern Asia possibly due to the low gluten consumption. This report is of a young female who presented with severe anaemia and hidradenitis suppurativa and was found to have coeliac disease. It is the first serologically confirmed adult case of the disease reported from Sri Lanka.

Case presentation: A 23-year-old female presented with a history of an acute febrile illness associated with cough for about 24 hours. She gave a background history of altered bowel habits for 2 years. A mixed deficiency anaemia was detected, and endoscopy, serology and histological tests confirmed a diagnosis of coeliac disease. She was successfully treated with a gluten free diet. She also had hidradenitis suppurativa which subsided with a gluten-free diet.

Conclusion: This case highlights an atypical presentation of anemia in coeliac disease in a population with low disease expression. Association of hidradenitis suppurativa with gluten hypersensitivity is an area of recent interest and complete resolution of the skin eruption occurred with a gluten free diet.

Keywords

Coeliac disease, Malabsorption, Gluten hypersensitivity

Abbreviations

CD: Coeliac Disease; IEL: Intraepithelial Lymphocytes; FBC: Full Blood Count; WBC: White Blood Cell Count; LDH: Lactate Dehydrogenase; TIBC: Total Iron Binding Capacity; TSAT: Transferrin Saturation; CRP: C Reactive Protein; ESR: Erythrocyte Sedimentation Rate; AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase; ALP: Alkaline Phosphatase; Gamma GT: Gamma Glutaryl Transferase; PT: Prothrombin Time; APTT: Activated Partial Thromboplastin Time; Anti-Dsdna: Anti Double Stranded Deoxyribonucleic Acid; HIV: Human Immunodeficiency Virus; TSH: Thyroid Stimulating Hormone; FBS: Fasting Blood Sugar; USS: Ultrasound Scan; MRI: Magnetic Resonance Imaging; HS: Hidradenitis Suppurativa; TTG: Tissue Transglutaminase; GFD: Gluten Free Diet; DXA: Dual Energy X-Ray Absorptiometry

Introduction

Coeliac disease is an immune mediated disease of the small intestine caused by sensitivity to dietary gluten in genetically predisposed individuals [1]. Serum antigliadin and antitransglutaminase antibodies are found in high titres. Symptoms as well as antibodies improve after removal of gluten from the diet. Gluten sensitivity is associated with skin and neurological manifestations independent of coeliac disease. The disease, as previously thought is not limited to individuals ethnically derived from Caucasian or European origin and is increasingly found in other populations [2]. However, there is only one case report of coeliac disease from Sri Lanka in the literature [3]. Recent data has shown improvement of hidradenitis suppurativa (HS) with dietary gluten exclusion [4]. However, there are no reported cases of HS associated with coeliac disease in the literature.

The case described here is a case of adult-onset

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coeliac disease in a 23-year-old female who presented with severe anaemia and HS.

Case Report

A 23-year-old female presented to us with a 24-hour history of fever associated with a non-productive cough. The fever was of low-grade intermittent nature and accompanied by chills but no rigors. She had 5-6 episodes of loose watery stools daily for 5 days. They were of small volume, not foul smelling or difficult to flush and had no blood or mucus. There was no history of recent food consumption from outside her home or of recent antibiotic use.

On further inquiry, she claimed to have had intermittent loose stools for the preceding 2 years. These bouts occured once or twice a month where she has 3-4 episodes of small volume loose stools per day lasting 2-3 days, on occasion associated with colicky abdominal pain. There was no blood or mucus, nocturnal or fasting diarrhoea and pica.

The review of systems was normal except for a recurring skin eruption involving the axillae and buttocks associated with pain and purulent discharge. There were no complains of long-term joint pains, dyspnoea or palpitations on exertion, yellowish discolouration of eyes associated with fever or other constitutional symptoms such as lethargy, night sweats or loss of appetite. There was no past or contact history of tuberculosis nor a history of high-risk sexual behaviours.

She was taking a normal Sri Lankan diet with three rice-based meals and daily intake of meat, fish, eggs and milk. However, she was having difficulty gaining weight since childhood though her height was normal. She denied use of laxatives or purgatives for intentional loss of weight. She is the first born to non-consanguineous parents. She has no family history of similar illnesses. She has regular menstruation with no menorrhagia or dysmenorrhea. She is a lifelong non-smoker and teetotaler.

On examination, she was thin built with a BMI of 14.71 kg/m^2 and pale. She was anicteric. She had glossitis and angular stomatitis, along with leukonychia. She had no lymphadenopathy. A papular rash was noted with some healed pustules over the buttocks and bilateral axillae. Cardiovascular system examination was normal with a pulse rate of 88 beats per minute and regular. Blood pressure was 110/70 mmHg. Heart was in dual rhythm with no murmurs. Abdominal, respiratory examination was normal as was the neurological examination with no evidence of peripheral neuropathy (Table 1).

Table 1: Summary of investigations.

Investigation	Result	Reference range
1. FBC		
WBC	$7.71^{*}10^{9}$/L	$4\text{-}11^{*}10^{9}$/L
Platelets	$387^{*}10^{9}$/L	$150\text{-}450^{*}10^{9}$/L
Haemoglobin	63 g/L	115-165 g/L
2. Reticulocyte index	1.42%	(0.2-2%)
3. LDH	210 U/L	125-220 U/L
4. Direct antiglobulin test	Negative	
5. Serum iron	28 microg/dL	60-180 µg/dL
TIBC	454 mcicrog/dL	274-385 µg/dL
TSAT	6.22%	15-30%
Serum Ferritin	122 microg/L	25-155µg/L
6. CRP	< 6 mg/dL	0-10 mg/dL
7. ESR	78 mm/1st hour	< 20/1st hour
8. Serum Sodium	135 mmol/L	135-145 mmol/L
Serum Potassium	4.5 mmol/L	3.5-5 mmol/L
Serum Creatinine	0.8 mg/dL	0.6-1.5 mg/dL
9. Serum Albumin	2.6 g/dL	3.5-5 g/dL
Serum Globulin	2.4 g/dL	2-3.5 g/dL
AST	63 U/L	10-40 U/L
ALT	70 U/L	5-30 U/L
ALP	45 U/L	25-100 U/L
Gamma GT	35 U/L	8-61 U/L
Total Bilirubin	0.6 mg/dL	0.5-2 mg/dL
10. PT	13s	12-14s
APTT	32s	30-46s

11. Serum calcium Serum phosphate	2.32 mmol/L 1 mg/dL	2.2-2.7 mmol/L 0.6-1.5 mg/dL
12. Serum Vitamin B12 level Serum folate- not available	< 61 µmol/L	(140-650 µmol/L)
13. Stool full report	No pus cells, red cells or fat globules	
14. Stool culture	No growth	
15. Stool occult blood*3	Negative	
16. Serum Tissue transglutaminase antibody	29.05 RU/ML	< 20RU/ML
17. Anti-Nuclear antibody	1/100	< 1/100
18. Anti dsDNA Anti-Smith antibody C3 C4	Negative Negative 87 mg/dL 45 mg/dL	 66-185 mg/dL 15-52 mg/dL
19. HIV 1 and 2 antigen and antibody	Negative	
20. Anti endomysial antibody	Negative	
21. Stool calprotectin	Not detected	50-120 µg/g
22. TSH	1 mIU/mL	0.4-4 mIU/mL
23. FBS	80 mg/dL	< 110 mg/dL
24. HbA1C	5%	< 6.5%
25. Chest Xray and USS abdomen	normal	
26. Mycoplasma antibodies	not detected	
27. CECT chest, abdomen and pelvis	normal	
28. MRI enteroclysis	normal	

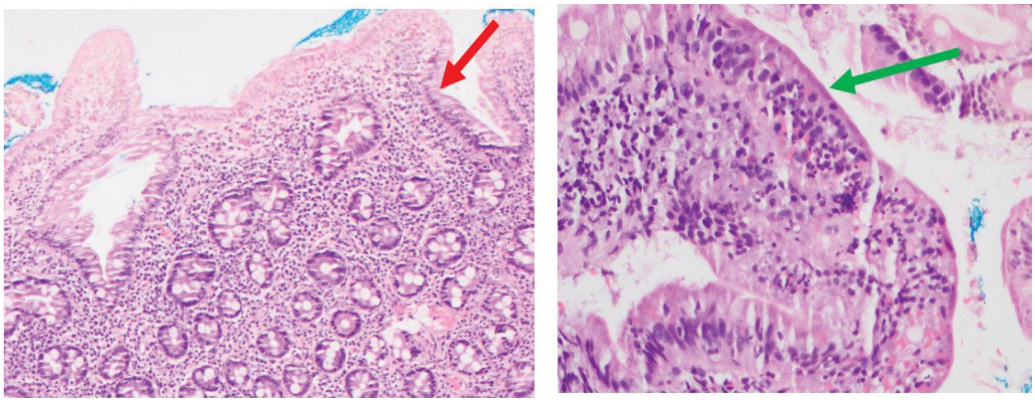

Figure 1: Duodenal biopsy showing increased intraepithelial lymphocytes (red arrow) and villous atrophy (green arrow).

The initial investigations showed a severe anaemia with a haemoglobin of 6.3 g/dL, with normocytic normochromic indices. Blood picture revealed a mixed picture with oval macrocytic cells and hypochromic microcytic cells. Few hyper segmented neutrophils were seen which was suggestive of mixed iron and B12 deficiency. Skin biopsy was taken from buttock rash which showed features suggestive of healed hidradenitis suppurativa.

As the initial management, she was transfused 2 units of red cell concentrate due to the severe anaemia. She was started on iron and folic acid supplementation along with IM vitamin B12 injections daily for 5 days. She was discharged on oral Clarithromycin 500 mg twice daily for 7 days.

On review after one-week ESR remained elevated at 90 mm and haemoglobin was 7.9 g/dL. A bone marrow biopsy was arranged which showed normocellular erythropoiesis with some dysplastic changes. Granulopoiesis and megakaryopoiesis were normal.

Upper GI endoscopy showed a normal oesophagus and stomach with erythematous areas seen in D1 and D2. Biopsies from D1 and D2 revealed a duodenal mucosa with active inflammation, partial villous atrophy and mildly increased intraepithelial lymphocytes. (25/100 enterocytes) Intestinal pathogens were not seen (Figure 1). Lower gastrointestinal biopsies were normal. She had positive anti tissue transglutaminase antibodies. A DXA scan was done and normal with a lowest Z score of -1.3 at left hip. She had an insufficient Vitamin D level

Table 2: Food to avoid in a gluten free diet.

Food to be avoided
Wheat, barley, rye, oats (Unless specified to be gluten free on the label)
Baked goods- Cookies, cake, pastries
Processed foods- Burgers, noodles, hotdogs
Snacks and condiments- Seasoned potato chips, French fries, sauces including soy sauce
Beverages- Beer, malted drinks, commercial chocolate drinks

of 15 ng/ml (20-100). A definitive diagnosis of coeliac disease was made.

She was managed in a multidisciplinary approach with involvement of the gastroenterologist, medical nutritionist and general physician. Her dietetic history was revisited to assess the exposure to gluten. A dietary recall showed that she takes 3 cups of milk per day with a malt containing supplement which contain gluten. She also takes processed foods such as burgers and snacks such as French fries about 3 times a week. She was advised on a lifelong gluten free diet (Table 2).

Her diet plan was prescribed taking into consideration the maintenance calorie requirement as well as the deficit. A total of 1400 kcal per day (40 kcal/kg/d) was given with 15% as protein. Her initial weight was 34 kg and ideal weight 56 kg. Target was 10% weight gain in 3-6 months. $FeSO_4$ 200 mg bd along with multivitamin 1 tablet per day were continued. She was reviewed in 2 months in the ward and had gained 2 kg. Haemoglobin was 11.2 and serum ferritin 239 micrmol/L. The skin rash had completely healed. A repeat upper GI and biopsy was planned for in 6 months.

Discussion

This young female presented with an acute respiratory illness associated with diarrohoea and pallor. Initially we considered a clinical diagnosis of atypical pneumonia. She had elevated inflammatory markers with normal platelet counts which was against a diagnosis of Mycoplasma infection where thrombocytopaenia is common. She had a normal chest radiograph which is another pointer against an atypical pneumonia. Further, the anaemia was not due to haemolysis as expected in Mycoplasma infection [5].

Malabsorption became a possibility given the long-standing history of altered bowel habits and poor weight gain along with findings of a mixed deficiency anaemia and hypoalbuminaemia. We suspected a diagnosis of celiac disease on the basis of duodenal biopsy which demonstrated partial villous atrophy and increased IELs classifying her as grade B1 on Corazza classification. In the presence of intermediate features as such, serology is key to differentiate from other conditions causing villous atrophy such as tropical sprue, small-bowel bacterial overgrowth, Whipple's disease, Crohn's disease, etc. [6]. Hence this was confirmed by positive anti tissue transglutaminase antibodies. Interestingly she had evidence of hidradenitis suppurativa which is known to be associated with gluten hypersensitivity although not classically described in CD [4,7].

Anaemia is a well-known feature of celiac disease, and the aetiology is multifactorial. It is often due to deficiency of iron, folate and vitamin B12 [8]. This patient had a mixed vitamin B12 and iron deficiency aneamia. Coexisting folate deficiency was a possibility. The cause for the anaemia was conventionally thought to be due to micronutrient deficiencies due to malabsorption itself [9]. The degree of iron deficiency correlates to degree of villous atrophy and improves with a gluten free diet supporting this mechanism. Serum ferritin levels may be low due to extreme deficiency in severe disease due to total loss of absorptive capacity or be elevated as a part of an acute phase reactant in less severe disease [10]. However, celiac disease is characterized by inflammation that is not confined to the intestine but also systemic. Hence hematologic manifestations of the disease are likely to reflect a combination of local and systemic factors [11].

Hidradenitis suppurativa which was found on the skin biopsy of our patient is not an extraintestinal manifestation described in celiac disease [9]. However, there are reports of improvement in HS with gluten free diet and gluten is the most commonly withdrawn food item by patients with HS [4]. In a review done in Germany to identify potential triggers in 40 patients with HS, 2 patients were found to have celiac disease with improvement of skin eruption after a GFD [7]. Our patient also had complete resolution of her HS when put on a gluten free diet suggesting an association of gluten hypersensitivity and HS. Claudio, et al. in a study where exclusion of brewer's yeast from the diet of patients with HS showed resolution of skin lesions suggest that *S. cerevisiae* which is a fungus in yeast that causes rising of wheat during fermentation mounts an immune response in patients with HS worsening the skin disease [12]. A possible explanation is that baked food constitutes most of the gluten in the diet and exclusion of baked products and thence the yeast used for rising rather than exclusion of gluten itself is responsible for the improvement. Recurrence of HS with gluten reintroduction in this patient could not be elicited as gluten rechallenge is not recommended in management of CD currently. Another postulated mechanism of HS was secondary infection of the skin caused by weakened immunity in CD. This is corroborated by

some evidence from metagenetic sequencing that has revealed an abundance of gram-negative bacteria as the predominant skin flora in patients with HS as opposed to staphylococcus species seen in normal individuals [13]. However, this hypothesis needs to be further explored.

CD is rare in Sri Lanka and there is a single case report published in 2011. The rarity could be because of the traditional diet of rice which accounts for 60-80% of cereal consumed in Sri Lanka [14]. One could postulate that the low gluten content fails to trigger an adequate autoimmune response to cause symptomatic disease.

Malabsorption develops when when there is failure of absorption of nutrients resulting from a multitude of causes which can be classified into three groups: (i) Maldigestion, due to defects in digestive enzymes; (ii) Mucosal or mural causes such as celiac disease (CD); and (iii) Microbial causes [5].

CD has an estimated prevalence of one percent in the world [15,16]. The current understanding for the wide spectrum of manifestations from asymptomatic to severe malabsorption is a complex interaction between genetic and environmental factors. Gluten is the protein fraction of wheat, rye and barley [1]. HLA-DQ2, HLA-DQ8, HLA-DR3-DQ2 and HLA-DR4-DQ8 genes are known to confer genetic susceptibility [17]. Antigen presenting cells that are positive for HLA- DR3-DQ2 and HLA-DR4-DQ8 present gluten peptides efficiently, thus initiating and driving the immune response, predominantly occurring in the lamina propria. The inflammatory response releases tissue transglutaminase (TTG); the highly specific endomysial auto-antigen. Deamidating or crosslinking of gluten peptides by TTG may further potentiate the antigen presentation. The result is lamina propria T-cell activation and mucosal transformation by activated intestinal fibro-blasts. This immune activation drives the destruction of enterocytes in intestinal villi resulting in impaired absorption [1,18].

Coeliac disease is associated with other autoimmune diseases, most commonly type 1 diabetes mellitus and autoimmune thyroid disease [19]. Our patient neither had a family member affected by the disease nor fulfilled criteria for an associated autoimmune disease. A positive antinuclear antibody (ANA), however was present. Although there have been postulations about increased prevalence of autoantibodies in patients with coeliac disease, studies up to now have shown similar prevalence of ANA in CD and general population [20].

Current understanding of CD is different from the traditionally defined malabsorptive disorder where many varied presentations can manifest at any age. Clinically three phenotypes of coeliac are seen; classical, atypical and silent [10]. Classical coeliac disease is characterized by symptoms and sequelae of gastrointestinal malabsorption [5]. Atypical disease manifests with minimum gastrointestinal symptoms and predominant extraintestinal features. Silent disease is where completely asymptomatic individuals have positive serology and villous atrophy on biopsy which is usually incidentally detected [10]. Our patient had atypical disease manifestation as she had mild chronic gastrointestinal symptoms and anaemia as a consequence of malabsorption.

Out of the extraintestinal manifestations, poor growth is the most frequent [21]. Others include anaemia [11], neurological manifestations such as peripheral neuropathy and gluten ataxia [22], elevated transaminases, dermatitis herpetiformis, osteoporosis and reproductive problems such as delayed puberty and subfertility [9].

The diagnosis of CD is confirmed with serology and upper endoscopy with histology of multiple biopsies of the duodenum in a patient with a clinical finding. Both American and British Gastroenterology Societies specify that the patient has to be on a gluten containing diet when performing serology and biopsy for coeliac disease [23-25]. IgA anti-tissue transglutaminase antibody is the single most preferred test for detection of CD serologically. If there is coexistent IgA deficiency, IgG-based testing should be done [24]. The sensitivity of the TTG-IgA for untreated CD is about 95%. It also has high specificity of 95% or greater [25]. However, if the suspicion of CD is high, it is recommended to pursue intestinal biopsy even if serologies are negative [24]. The characteristic histological features of CD on an intestinal biopsy are blunted or atrophic villi, crypt hyperplasia, lymphocytic infiltration in the lamina propria, structural abnormalities in epithelial cells and intraepithelial lymphocyte (IEL) infiltration. The first and most sensitive marker of gluten sensitivity on the small bowel mucosa is increased IELs. Multiple biopsies are imperative for diagnosis as intestinal involvement is patchy [26,27]. Corazza classification describes the histological changes in CD which take into consideration the presence of increased intraepithelial lymphocytes, crypt hyperplasia and villous atrophy [28].

A diet free of gluten remains the only effective treatment for CD at present. This involves avoiding wheat, barley and rye. Although the term “gluten free” implies total elimination of all sources of gluten, in practice it is a diet containing gluten at such low levels insufficient to mount hypersensitivity [24]. GFD results in resolution of symptoms and reversal of intestinal damage in most individuals. Failure to comply with GFD carries risk of morbidity and mortality. Risk of malignancy is increased (e.g., adenocarcinoma of small bowel, oesophageal carcinoma, B-cell and T-cell non-Hodgkin lymphomas, intestinal T-cell lymphomas) in patients with active CD [9].

American Society of Gastroenterology recommends long term follow-up of CD patients by a dietician experienced in coeliac disease management with periodic medical reviews. Objective of regular follow-

up is to monitor and ensure adherence tom GFD and monitoring for disease activity and micronutrient deficiencies. Monitoring of adherence to GFD is based on a combination of history and serology. For cases with lack of response of symptoms despite GFD, upper GI endoscopy with intestinal biopsies is recommended for monitoring [24].

Accordingly, our patient was regularly followed up by the medical nutritionist and reviewed by the gastroenterologist. Vitamin D levels were repeated in 3 months after treatment which had normalized, and supplementation was continued at 1000 IU/day. Her vitamin B12 level also normalized. Yearly DXA scan was planned.

Conclusion

This case of coeliac disease presenting with anaemia highlights the need for suspicion of a disease that is considered a rarity in our population. Moreover, it raises the awareness that the true prevalence of the disease is underestimated due to the high number of cases without GI symptoms.

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