Celiac Disease with Pure Red Cell Aplasia: An Unusual Hematologic Association in Pediatric Age Group

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Abstract Anemia in Celiac disease (CD) is usually hypoproliferative, reflecting impaired absorption of essential nutrients like iron and various vitamins. We report a 2-year-old boy with Celiac disease and severe anemia due to pure red cell aplasia, diagnosed by bone marrow biopsy. This rare, unexplained extra digestive manifestation responded to gluten free diet.

Keywords Pure red cell aplasia · Celiac disease · Bone marrow biopsy · Gluten free diet

Introduction

Celiac disease (CD) is an immune-mediated systemic disorder elicited by gluten and related prolamines in genetically susceptible individuals [1]. The spectrum of presentation can be from an asymptomatic child with only positive serology to a wide range of clinical features both due to intestinal and extra intestinal involvement. The extra intestinal manifestations involve almost all organ systems [2]. The incidence of anemia varies greatly from 12 to 69 % of newly diagnosed patients with CD. This anemia is usually hypo proliferative, reflecting impaired absorption of essential nutrients like iron and various vitamins [3]. Anemia due to pure red cell aplasia (PRCA) is rare [4]. We

report fourth case of CD and severe anemia due to PRCA, an unusual association in pediatric age group.

Case History

A 2-year-old male child born out of non consanguineous marriage, at term without any significant antenatal history presented in the OPD with paleness, failure to thrive and repeated bulky, foul smelling stool for last one and half year. There was history of four transfusions of packed red cells since seven month of age. There was delay in achievement of motor and social milestones and eruption of teeth. Dietary history suggested no calorie or protein deficit. There was no history of bleeding from any site. On examination, he was irritable and sick looking. There was severe pallor without any lymphadenopathy, icterus, clubbing or edema. Signs of severe protein-energy malnutrition like glossitis, angular stomatitis and multiple aphthous ulceration, fuzzy depigmented hair, delayed dentition, xerotic and inelastic loose folds of skin in the groin and buttock were noted. His weight and height were 7 kg(<3rd percentile) and 87 cm(<50th percentile). Systemic examination revealed generalised mild hypotonia and muscle atrophy but was otherwise unremarkable.

Complete hemogram were as follows: MCV 89.1 fl, MCH 31 pg, MCHC 33 % with anisocytosis, mildly increased red cell distribution width 16.7 %, total leukocyte count 8,600/mm³, differential count(N₅₅ %, L₃₉ %, M₂ %, E₄ %), platelet count 1.6 lakh/mm³ and corrected reticulocyte count 0.35 %. Erythrocyte sedimentation rate (ESR) and C-reactive protein were high. Apart from markedly raised serum ferritin (16227 ng/ml), iron studies and thyroid function tests were normal. Hepatic and renal functions were within normal limits. Anti nuclear factor, Anti ds-DNA, and Direct Coombs test were negative. Urine and

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Fig. 1 Duodenal biopsy section shows classical pattern of crypt hyperplasia, villous atrophy, intraepithelial lymphocytosis suggestive of celiac disease (H&E, $\times 40$)

stool examination revealed no abnormality. HIV serology, sputum for acid fast bacilli and Mantoux test were negative. Screening of Hep B, C and parvoviral IgM were negative. Upper gastrointestinal endoscopy revealed scalloping of duodenal folds especially at the 2nd part, a feature suggestive of celiac disease. Biopsy taken from different quadrants of duodenum showed a classical pattern of villous atrophy, crypt hyperplasia with intraepithelial lymphocytosis (Marsh IIIc) (Fig. 1). Quantitative estimation of serum IgA anti-tissue transglutaminase found to be elevated (198 IU/ml, normal range <20 IU/ml). Bone marrow examination showed normal marrow cellularity with M-E ratio 40:1, markedly depressed erythropoiesis with normal other series without any abnormal cell or parasite suggestive of PRCA (Fig. 2). Radiograph of long bones showed generalized demineralization which was confirmed by DXA scan 0.408 g/cm^2 and Z score of -1.7 (-1 to -2 low normal). Chest X-ray revealed no thymic shadow or mediastinal widening. The diagnosis therefore was celiac disease with protein energy malnutrition grade IV. He was managed for severe malnutrition as per guidelines followed by dietary restriction of gluten based diet and supplementation of vitamins and minerals. Stool character improved within 2 weeks.

After 1 year of follow up he had gained weight of about 3 kg (<3 rd centile) with same height and episodes of loose motion decreased. He began to stand with support without any signs of nutritional deficiency. Pallor recurred which required packed red blood cell transfusion once a year and serum ferritin was reduced to 362 ng/ml.

Fig. 2 Bone marrow biopsy section shows normocellular marrow, normal granulopoiesis, adequate no of megakaryocytes, myeloid maturation is sequential and erythropoiesis is depressed suggestive of Pure Red Cell Aplasia (RE stain, $\times 40$)

Discussion

Several classifications of CD have been used, the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) working group decided to revise the classification into classical, atypical, asymptomatic, latent, and potential CD. Because atypical symptoms may be considerably more common than classic symptoms, the group decided to use the following terminology: gastrointestinal symptoms and signs (e.g., chronic diarrhea) and extra intestinal symptoms and signs (e.g., anaemia, neuropathy, decreased bone density, increased risk of fractures) [1]. The prevalence of anemia varies greatly according to different reports and has been found in 12 to 69 % of newly diagnosed patients with CD [3]. Studies using serologic tests and small-bowel biopsies in patients referred for evaluation of iron deficiency anemia have reported CD in 0 to 8.7 % of patients. These studies are heterogeneous in design and used different methods for diagnosis of CD, often in selected referral populations [3, 5]. Anemia secondary to malabsorption of iron, folic acid and/or vitamin B12 and other micronutrient deficiency e.g. copper etc. are common complication of CD nevertheless anemia of chronic disease is one of the most important entity determine the severity of the anemia [3]. Anemia of chronic illness is usually mild (7–9 g/dl). Our child had severe anemia of 6 g/dl. Apart from an increase in the acute phase reactant ferritin, iron studies were normal. Hence anemia of chronic disease and iron deficiency

anemia were ruled out in this case. Transient erythroblastopenia (TEC) which lasted for a duration varying from few weeks to 2 months. The diagnosis was confirmed by spontaneous recovery of the marrow with resolution of anaemia. In our case anemia was persisting after one year of follow up. Diamond Blackfan Syndrome which is usually seen in children less than 1 year of age with frequent congenital anomalies and is not associated with spontaneous recovery [4].

There are previous reports of PRCA associated with celiac disease [6]. Only three pediatric cases have been reported in the literature suggesting the possibility of a probable new association. This report also points that PRCA may be another extra intestinal manifestation of celiac disease and should be considered when severe anemia develops in the absence of blood loss or hemolysis.

Although the patho-physiology of acquired PRCA seems heterogeneous, several published data suggest that autoimmune mechanisms underlie most PRCA cases [4]. In some cases, immunoglobulins molecules against erythropoietin at erythropoietin-responsive erythroid precursor cells, or against erythroblasts themselves may block the effect of erythropoietin or destroy erythroid cells [7]. Where plasma inhibitor of erythropoiesis cannot be determined, cellular immunity may play a role in the pathogenesis of PRCA. T cells or natural killer cells have been proposed to secrete factors selectively inhibiting erythropoiesis. Lysis of erythroblasts can be induced by T-cells resulting from classic T cell receptor (TCR)-mediated antigen recognition, or by natural killer cells mediated by major histocompatibility complex (MHC) unrestricted effector-target cell recognition because erythroid precursors progressively lose expression of MHC class I [8].

The hallmark of CD is an immune-mediated enteropathy that involves both the innate and adaptive immune system. Paracellular passage of gliadin peptides (α -gliadin 31–43) has been shown to induce apoptosis of enterocytes, upregulate MHC class I molecules, activate MAP kinase pathway, and upregulate expression of CD83, a maturation marker of dendritic cells [9, 10]. This peptide, and others, enhances IL15 production leading to an expansion of intraepithelial lymphocytes (IELs) and triggering the innate immune system. IL15 plays a key role in enhanced cytolytic activity of IELs via induction of NK receptors on the IEL and also contributes to promoting the CD4+ T cell adaptive response [11].

The association between PRCA and CD remains unclear. PRCA which is immunopathogenically correlated, may be a further manifestation in the spectrum of autoimmune disease associated with this genotype.

A high serum ferritin and ESR can significantly show the underlying disease activity as evidence of systemic inflammation [12] as in our case it was very high initially

and over the time following gluten restriction it came down near to baseline level. In the patient described here, gluten free diet improved symptoms attributable to CD due to normalization of the small intestinal mucosa, like previous case of Couderc et al. [6]. Scott and Losowsky [13] thought that some immunological disorders in patients with celiac disease might improve with a gluten free diet. Our patient whom blood transfusion requirement was reduced might be explained by this hypothesis. To date, only hypotheses exist to explain the concordance of separate autoimmune diseases in individuals [14].

To conclude, PRCA although less common, could represent an extra intestinal manifestation occurring in celiac disease, but this will need to be confirmed by further study.

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