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Investigation of celiac disease followed by immune thrombocytopenic purpura diagnosis in patients and comparison with literature

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ABSTRACT

OBJECTIVE: Celiac disease (CD) and Immune thrombocytopenic purpura (ITP) may occur together as a result of similar autoimmune mechanisms. The aim of this study was to assess the frequency of CD in a group of ITP patients and in the literature.

METHODS: A total of 29 patients in Pamukkale University Faculty of Medicine Hospital Pediatric Hematology and Oncology Department with ITP were included in the study. Test was performed for the antibodies related to CD. Positive result for celiac antibodies was confirmed with biopsy. The results were compared with the literature.

RESULTS: Of the study group, 13 patients (44.8%) were female and 16 (55.2%) were male. The mean age was 7.2±4.7 years and mean platelet count at the time of admission was 13,440±11,110/mm^3 (range: 2000-41,000/mm^3). Twelve patients (41.4%) were diagnosed as acute ITP, 6 patients (20.7%) as persistent ITP, and 11 patients (37.9%) as chronic ITP, according to the duration of thrombocytopenia. Antibody positivity was detected in 1 patient. Histological evaluation was compatible with CD. Results were compared with studies regarding the prevalence of CD in the population. No significant difference was found.

CONCLUSION: Although it is not necessary to perform CD test in every case of ITP, the presence of differential diagnosis of CD is important to prevent unnecessary treatment, especially in ITP patients with growth retardation or malabsorption findings.

Keywords: Autoimmunity; celiac disease; immune thrombocytopenic purpura.

Immune thrombocytopenic purpura (ITP) is the most frequent cause of sudden onset thrombocytopenia in healthy children. In children, it usually emerges after an infection or a vaccination. It is an acquired disease, coursing with thrombocytopenia developing as an outcome of a decrease in the lifespan of platelets caused by autoantibodies formed against platelets [1, 2].

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Celiac disease (CD) is an immunological disease induced by intolerance of the small bowel to gluten. Growth retardation and chronic diarrhea are the most frequently seen manifestations [3]. In addition to the typical findings of malabsorption, many autoimmunological disorders may accompany the disease, or there may be extraintestinal findings, such as growth retardation, developmental delay, impaired hepatic function, skin manifestations, osteoporosis, or hematological disorders [4, 5]. As a result of having similar autoimmune mechanisms, in some publications, CD has been reported as a risk factor for ITP [6]. The aim of this article was to evaluate the frequency of CD in a group of patients and compare the results with literature data.

MATERIALS AND METHODS

A total of 29 patients with a diagnosis of ITP whose follow-up and treatment were ongoing at the Department of Pediatric Hematology and Oncology of the Pamukkale University Faculty of Medicine were included in the study. CD manifestations, and anti-endomysial antibody (EMA), tissue transglutaminase antibody (tTG), and immunoglobulin A (IgA) levels were evaluated. Age, gender, platelet count at the time of admission, and duration of thrombocytopenia were recorded. Based on the duration of the disease, thrombocytopenia was classified as acute (<3 months), persistent (3–12 months), or chronic (>12 months) thrombocytopenia. EMA and tTG positivity was confirmed with endoscopic examination and histological analyses. The results were compared with literature data. The study was approved by the ethics committee of Pamukkale University (2017/01–10.01.17). Written, informed consent was obtained from the parents of all patients.

Statistical analyses

All descriptive statistical analyses were performed using IBM SPSS Statistics for Windows, Version 22.0 (IBM Corp., Armonk, NY, USA). Fisher chi-square test was used for the comparison of categorical variables.

RESULTS

Thirteen female (44.8%) and 16 male (55.2%) patients with a collective mean age of 7.2±4.7 years (range: 7 months-17 years) were included in the study. Mean platelet count at admission was 13,440±11,110/mm^3 (range: 2000–41,000 mm^3). The type of ITP was classified based on the duration of thrombocytopenia as acute (n=12; 41.4%), persistent (n=6; 20.7%), or chronic (n=11; 37.9%). Clinical and laboratory characteristics of the patients are provided in Table 1.

Examination for the presence of CD revealed tTG IgA: 24.1 U/mL (<20 U/mL) and EMA positivity in 1 patient, a 9-year-old female with weight of 22 kg (3–10 percentile) and height of 118 cm (<3 percentile). Some notable laboratory parameters were as follows: white blood cell count: 6360/mm^3, hemoglobin: 11.4 g/dL, platelet count: 28,000/mm^3, aspartate aminotransferase: 174 IU/L, alanine aminotransferase: 193 IU/L, lactate dehydrogenase: 914 U/L, ferritin: 42 ng/mL, iron: 38 ug/dL, total iron binding capacity: 300 ug/dL, vitamin B12: 284 pg/mL, folate: 9.9 ng/mL, prothrombin time: 12.1 seconds, partial thromboplastin time: 28 seconds, international normalized ratio: 1.08, free thyroxine: 1.39 ng/dL, and thyroid stimulating hormone: 3.21 uIU/mL. In addition to thrombocytopenia, the patient had impaired liver function and growth retardation. On peripheral smear, no atypical cells or blast cells were seen, and an average of 2 platelets were noted in every microscopic field of view. Histopathological examination of bone marrow aspiration biopsy specimen revealed an increase in the number of immature-mature megakaryocytes without any blast cells. The patient underwent endoscopic biopsy with the initial diagnosis of CD, and histopathological analysis revealed the presence of severe mucosal injury, villous atrophy, increase in the number of intraepithelial lymphocytes, and cryptic hyperplasia (Figure 1). Histopathological diagnosis was reported as consistent with Stage 3c CD based on modified Marsh classification. No treatment was administered due to the lack of

Table 1. Characteristic features of the study participants

Patient no.	Gender	Age	Platelet count (/mm^3)	Duration of thrombocytopenia	tTG Ig A level (U/mL)	Ig A level (mg/dL)	Type
1	Female	9 years	28,000	5 months	24.2	420	Persistent
2	Female	15 years	11,000	1 month	2.94	48	Acute
3	Female	8 years	31,000	17 months	5.2	301	Chronic
4	Female	9 years	7000	2 months	1.19	74	Acute
5	Male	4 years	1000	1 month	0.99	38	Acute
6	Male	7 months	16,000	6 months	0.96	36	Persistent
7	Male	2 years	24,000	1 month	0.45	42	Acute
8	Male	4 years	25,000	1 month	1.66	44	Acute
9	Male	10 years	20,000	6 months	0.74	90	Persistent
10	Female	6 years	21,000	1 month	0.65	106	Acute
11	Male	16 years	2000	18 months	0.89	148	Chronic
12	Male	3 years	3000	1 month	1.13	149	Acute
13	Male	4 years	9000	8 months	3.1	47	Persistent
14	Male	10 years	15,000	3 years	1.69	253	Chronic
15	Male	1 year	11,000	1 year	0.89	86	Chronic
16	Female	15 years	2000	1 month	2.06	71	Acute
17	Female	9 years	9000	2 years	1.04	105	Chronic
18	Female	5 years	3000	1 month	2.1	162	Acute
19	Male	3 years	4000	4 years	1.72	67	Chronic
20	Female	8 months	41,000	18 months	3.2	72	Chronic
21	Female	6 years	2000	6 months	1.39	168	Persistent
22	Female	9 years	29,000	6 months	1.55	80	Persistent
23	Female	10 years	15,000	1 month	4.44	142	Acute
24	Male	17 years	29,000	5 years	3.12	99	Chronic
25	Female	7 years	4000	2 years	4.97	93	Chronic
26	Male	3 years	15,000	1 month	2.17	33	Acute
27	Male	4 years	1000	2 months	3	138	Acute
28	Male	8 years	2000	4 years	1.39	217	Chronic
29	Male	12 years	10,000	18 months	1.2	113	Chronic

Ig A: Immunoglobulin A; tTG: tissue transglutaminase.

any finding of active bleeding and platelet count greater than 10,000/mm^3. The patient was started on a gluten-free diet. One month later, platelet count had risen to 87,000/mm^3. At fifth month of dietary therapy, platelet count of the patient was within normal limits.

In our study, the frequency of CD observed in our ITP patients was not significantly different from the results of previously performed studies related to the incidence of CD (Table 2).

DISCUSSION

In cases of CD, generally, the clinical findings become manifest due to intestinal mucosa injury and resultant malabsorption [7]. As a result of deficient intestinal absorption, and as an autoimmune disease, various hematological symptoms can be seen in CD. Treatment-resistant iron deficiency is the most frequently seen hematological disorder seen in atypical CD [7, 8]. In addition to iron deficiency,

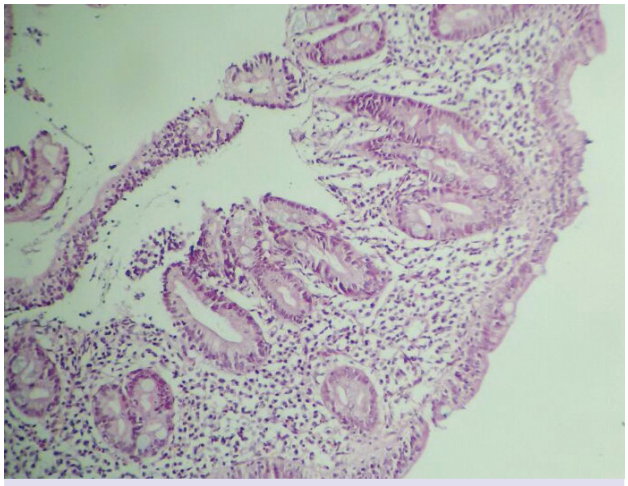

FIGURE 1. Histopathological examination of the biopsy material of the patients revealed villous atrophy, increase in the intraepithelial number of lymphocytes, and cryptic hyperplasia.

folic acid, and vitamin B12 deficiencies may be also seen [7]. In a study performed in our country, 21 of 22 patients diagnosed as CD, iron deficiency anemia was detected. Among them, 7 also had vitamin B12 deficiency, and folic acid deficiency was observed in 1 patient [9]. In CD, apart from anemia, leukopenia and thrombocytopenia may develop due to vitamin B12 and folic acid deficiencies, and immune cytopenias, such as ITP, can develop via different autoimmune mechanisms [8].

Concomitancy between CD and ITP was first described in 1988, and studies performed have demonstrated the presence of similar autoimmune mechanisms in the pathogenesis of both diseases [10]. It has been determined that the native immune system is important in the pathogenesis of CD, and that toll-like receptors (TLRs) also play a key role [11]. Zanoni et al. [12] demonstrated that in some cases of CD, tTG antibodies induce TLR4 activation. Presumably, TLR4 expression in platelets leads to thrombocytopenia [13].

CD is a frequently seen disease in the community; however, diagnosis can be overlooked due to its multivariant symptoms [14]. In a study performed in our country that screened 20,190 children, CD prevalence was detected at 0.47% [15]. Demirçeken et al. performed a study of tTG antibodies among healthy children aged 2 to 18 years who presented at the hospital, and found a prevalence of CD of 1% [16]. In another study performed in Turkey, CD was detected in 11 of 1263 children [17]. Cilleruelo et al. [18] evaluated 1291 newborns, and antibody positivity was found in 19 cases; 15 were diagnosed as CD based on histopathological evaluation of biopsy specimen. Prevalence of CD was found to be 1.1%. As an outcome of our study, among 29 ITP patients, antibody positivity and histopathological diagnosis of CD was detected in 1 patient. A significant difference was not found when our results were compared with literature data.

In cases of ITP associated with CD cited in the literature, an increase in platelet count to normal limit within an average of 1 year was observed with gluten-free diet and without the need for intravenous immunoglobulin or steroid treatment [19].

TABLE 1. Comparison of our results with results of other studies

	Number of patients with CD	Number of patients without CD	Total number of patients	Frequency %	p
Present study	1	28	29	3.4	
Dalgıç et al.	95	20,095	20,190	0.5	p=0.129
Demirçeken et al.	10	990	1000	1	p=0.271
Ertekin et al.	11	1252	1263	0.8	p=0.239
Cilleruelo et al.	15	1276	1291	1.1	p=0.301

p<0.05 significant; CD: Celiac disease.

In our patient, platelet count 1 month after initiation of gluten-free diet was 87,000/mm^3, and at 5 months, value was normal.

In conclusion, ITP is one of the atypical findings of CD that may accompany CD due to a similar autoimmunme mechanism. Although investigation for CD is not required in every case diagnosed as ITP, in ITP patients with developmental retardation or malabsorption, considering CD in the differential diagnosis is important so as to prevent unnecessary treatment.

Conflict of Interest: None declared.

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