**Clinical Biochemistry**
Case Report – 48752

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# A rare association: celiac disease and multiple myeloma in an asymptomatic young patient

## Asemptomatik genç bir hastada çölyak hastalığı ve multipl myelom'un nadir birlikteliği

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**Abstract:** Celiac Disease (CD) is a gluten-sensitive enteropathy, and an autoimmune disorder involving an innate and adaptive immune response that occurs in genetically predisposed patients who are exposed to gluten-containing foods and other environmental factors. Early diagnosis and treatment are essential in preventing complications of the disease. Symptoms may appear both in childhood or adulthood by the ingestion of gluten and are usually characterized by gastrointestinal symptoms; however, the diagnosis may be delayed because of various extraintestinal manifestations, such as iron deficiency anemia, osteoporosis, or non-specific skin lesions in adult patients. Although CD has been shown to have an increased risk of all malignancies, plasma dyscrasias, especially multiple myeloma (MM) associations, are rare and reported to be seen in elderly patients. The current report presents a 42-year-old female patient with a recent dysphagia after a hot food ingestion with no other complaints. Laboratory investigations revealed a mild anemia and high serum protein levels. CD was diagnosed after a small bowel biopsy and MM was diagnosed after a serum protein electrophoresis with immunotyping studies (IgA lambda as the monoclonal protein) and bone marrow biopsy. In the laboratory, Immunotyping studies of monoclonal protein included two alternative methods; Immunofixation electrophoresis and immunosubtraction method with capillary electrophoresis. Our patient, is young to have MM, since the median age at diagnosis of MM is 66 years and only 2% of patients are younger than 50 years. We believe that celiac disease played a significant role in the development of MM in this particular patient with IgA monoclonality and conclude that CD patients, even if they are young, must be monitored for plasma dyscrasias in addition to other malignancies.

**Keywords:** Celiac disease, Multiple myeloma, Gluten-sensitive enteropathy

**Özet:** Çölyak Hastalığı (ÇH) glutene duyarlı bir enteropatidir, genetik yatkınlığı olan bireylerde gluten maruziyeti ve çevresel faktörlerin de etkisiyle doğal ve adaptif immun sistemin yer aldığı oto immun bir hastalıktır. Erken tanı ve tedavi, hastalığın komplikasyonlarının önlemesinde önemlidir. Semptomlar, gluten alımına bağlı olarak çocukluk ya da erişkinlikte görülebilir ve genellikle gastrointestinal semptomlar ile karakterizedir, ancak tanı, demir eksikliği anemisi, osteoporoz veya erişkin hastalarda non-spesifik deri lezyonları gibi çeşitli ekstraintestinal bulgulardan dolayı gecikebilmektedir. Çölyak hastalarında tüm malignite risklerinin arttığı gösterilmekle birlikte plazma diskrazileri, özellikle multiple myelom (MM) birlikteliği nadirdir ve daha yaşlı hastalarda görülebildiği bildirilmiştir. Bu raporda, son günlerde gelişen,

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sıcak yemek sonrası ortaya çıkan disfaji şikayetinden başka bulgusu olmayan, 42 yaşında bir kadın hasta sunulmaktadır. Laboratuvar incelemelerinde hafif anemi ve yüksek serum protein düzeyleri saptanmıştır. Çölyak hastalığı tanısı endoskopi ve barsak biyopsisi sonrasında, MM tanısı ise protein elektroforezi ve immünolojik çalışmalar sonucunda (Monoklonal IgA lambda), ayrıca kemik iliği biyopsisi sonrasında konulmuştur. Laboratuvarda monoklonal proteinin immunolojik tiplendirilmesinde, iki alternatif metod kullanılmıştır: İmmunofiksasyon elektroforezi ve kapiller elektroforez/immunoçıkarım yöntemi. Hastamız, MM tanısı almak için oldukça gençtir, ilk defa MM tanısı alan hastaların median yaşları 66 dır ve hastaların sadece %2'si 50 yaş altındadır. IgA monoklonalitesi olan bu hastada, erken MM gelişmesine altda yatan Çölyak hastalığının rolü olduğuna inanmaktayız ve Çölyak hastalarında yaşları genç bile olsa diğer maligniteler izlenirken, plazma diskrazilerin de araştırılması gerektiğini düşünmekteyiz.

**Anahtar Kelimeler:** Çölyak hastalığı, Multiple myelom, Glutene duyarlı enteropati

# 1 Introduction

Celiac disease (CD-Celiac sprue) is a gluten-sensitive enteropathy and the most common food intolerance in the world that includes nearly 1% of the general population [1]. Symptoms of the disease appear by the ingestion of gluten, which is the major protein of wheat, barley, and rye. The clinical presentation of CD varies, and presents with non-specific symptoms such as abdominal bloating, diarrhea, pale stools, iron deficiency anemia, failure to thrive in children, fatigue, osteoporosis, short stature, unexplained increased liver enzyme levels, arthritis, myalgia, female infertility in adults, skin disorders, and neurologic abnormalities [1]. CD can occur in people of any age and it affects both genders. Genetic variables contribute 40% to the risk of developing CD and HLA class II haplotypes DQ2 and DQ8 are found to be the best characterized predisposing factors [1]. The frequency of CD increases by 10% in patients with a first-degree family member with CD [2]. A small bowel biopsy is the gold standard for diagnosis with serologic tests of anti-tissue transglutaminase IgA and IgG and endomysial antibodies. A gluten-free diet, as therapy, results in dramatic improvement, in both pathological and clinical findings.

Various intestinal malignancies have been shown to be associated with CD, but association with hematologic malignancies, especially plasma cell dyscrasias, are rare [3]. Multiple myeloma (MM) is one of the plasma cell dyscrasias, which is a malignant neoplasm that generates 10% of hematologic malignant disorders [4]. MM is a malignant clonal neoplasm of the plasma cells, originating from B-lymphocytes and characterized by an overproduction of monoclonal immunoglobulins [5]. The median age at diagnosis is 66 years, and only 2% of patients are younger than 50 years; MM is shown to be slightly more common in males [5]. Fatigue and bone pain are the most common symptoms of MM [5] with undefined anemia, which leads to fatigue. Other manifestations of MM are osteolytic skeletal lesions, hypercalcemia, and elevated serum creatinine levels [4]. In serum or urine protein electrophoresis, a narrow band is characteristic, which is referred to as a monoclonal band or M protein and is classified by its immunoglobulin components. The most commonly seen M proteins are IgG 50%, IgA 20%, Ig light chain only 20%, IgD 2%, and IgM 0.5% [4].

The current study presents a 42-year-old female patient with CD, who has been recently diagnosed with multiple myeloma, and had no symptoms other than mild anemia and dysphagia. The association of CD and MM is rare, and the patient's age is too young for MM onset. This study discusses the effects of autoimmune diseases such as CD on the incidence and survival in MM. It will also compare two alternative immunotyping methods to determine the M proteins: immunofixation electrophoresis with agarose gel (IFE) and capillary zone electrophoresis (CZE)/immunosubtraction method.

## 1.1 Case Report

A previously healthy 42-year-old female patient was admitted to Acıbadem University Hospital in November 2015 with complaints of dysphagia, which started three days prior after hot food ingestion. Her systemic symptoms revealed only gastroesophageal reflux disease. Her initial physical examination was normal. There was no history of previous illness, or smoking or alcohol intake. The family history had no remarkable features. In her upper gastrointestinal endoscopic evaluation, the esophageal mucosa was totally normal. There was a small hyperemic area on the antrum mucosa and the duodenum mucosa showed scalloping of the folds, fissures, and mosaic appearance (Figure 1). In order to eradicate eosinophilic esophagitis and duodenal atrophy, multiple esophageal and duodenal biopsies were taken. The histopathological examination of the duodenum revealed patchy intraepithelial lymphocytosis, the areas of total and subtotal villous atrophies and crypt hyperplasia. Histopathologic findings led to the

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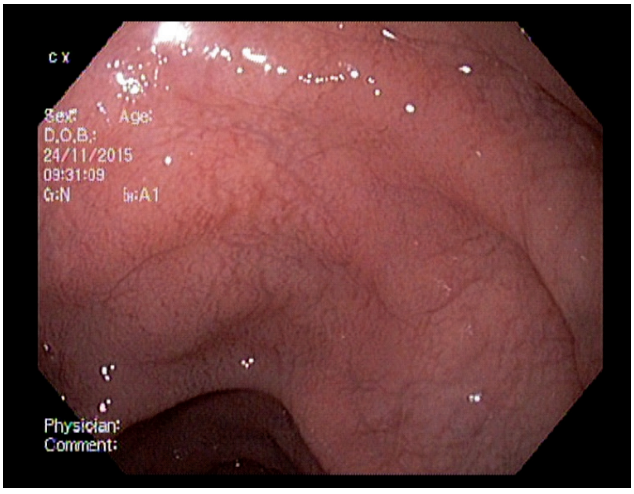
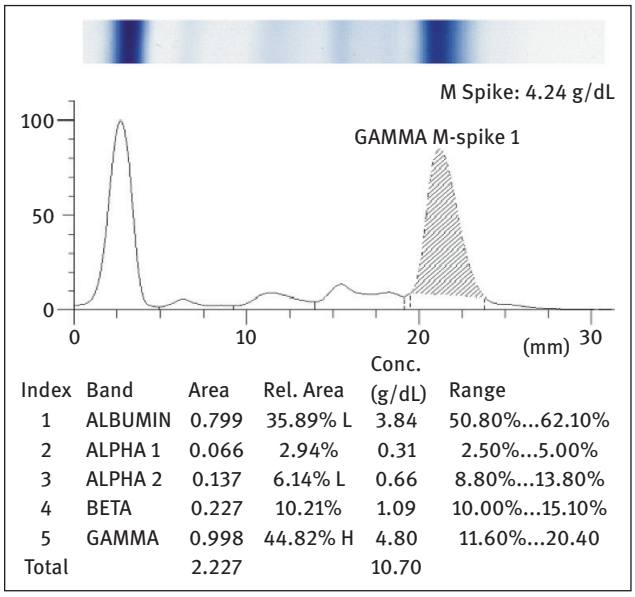



**Figure 1:** Endoscopic view of the duodenum showing fissure and scalloping, mosaic appearance of the folds.




| Index | Band | Area | Rel. Area | Conc. (g/dL) | Range |
|---|---|---|---|---|---|
| 1 | ALBUMIN | 0.799 | 35.89% L | 3.84 | 50.80%...62.10% |
| 2 | ALPHA 1 | 0.066 | 2.94% | 0.31 | 2.50%...5.00% |
| 3 | ALPHA 2 | 0.137 | 6.14% L | 0.66 | 8.80%...13.80% |
| 4 | BETA | 0.227 | 10.21% | 1.09 | 10.00%...15.10% |
| 5 | GAMMA | 0.998 | 44.82% H | 4.80 | 11.60%...20.40 |
| Total | | 2.227 | | 10.70 | |

**Figure 2:** Protein electrophoresis by agarose gel showed a remarkable M protein in the gamma region.

**Table 1:** Laboratory investigation results at celiac disease diagnosis.

| Test name (Unit) | Result | Reference range |
|---|---|---|
| Hemoglobin (g/dL) | 9.1 | 11.5–15.5 |
| Hemotocrit (%) | 29.2 | 35.5–48 |
| MCV (fL) | 74.9 | 80–95 |
| Iron (ug/dL) | 21 | 50–150 |
| Total Iron Binding Capacitiy (ug/dL) | 347 | 250–450 |
| Ferritin (ng/mL) | 6 | 10–291 |
| Vitamin B12 (pg/mL) | 326 | 200–835 |
| Folic Acid (ng/mL) | 3.6 | >5.38 |
| Urea (mg/dL) | 10 | 13–43 |
| Creatinine (mg/dL) | 0.68 | 0.6–1.0 |
| ALT (U/L) | 56 | 14–59 |
| Total Protein (g/dL) | 11.4 | 6.4–8.2 |
| Albumin (g/dL) | 2.94 | 3.4–5 |
| Calcium (mg/dL- Corrected for albumin) | 9.82 | 8.5–10.5 |
| Beta-2 microglobulin (mg/L) | 3.26 | 1.09–2.05 |
| IgA (mg/dL) | 5894 | 40–350 |
| IgG (mg/dL) | 201 | 690–1600 |
| IgM (mg/dL) | <8 | 50–300 |
| Free Kappa, serum (mg/L) | 0.69 | 3.3–19.40 |
| Free Lambda, serum (mg/L) | 81.66 | 5.71–26.3 |
| Gliadin Antibodies IgA (U/mL) | 17.9 | <12 |
| Gliadin Antibodies IgG (U/mL) | 26.5 | <12 |
| Transglutaminase Antibodies IgA (U/mL) | >300 | <12 |
| Transglutaminase Antibodies IgG (U/mL) | 51.1 | <12 |
| Endomysium Antibodies IgA (Titer) | 1:32 | <1:10 |
| Endomysium Antibodies IgG (Titer) | 1:320 | <1:10 |

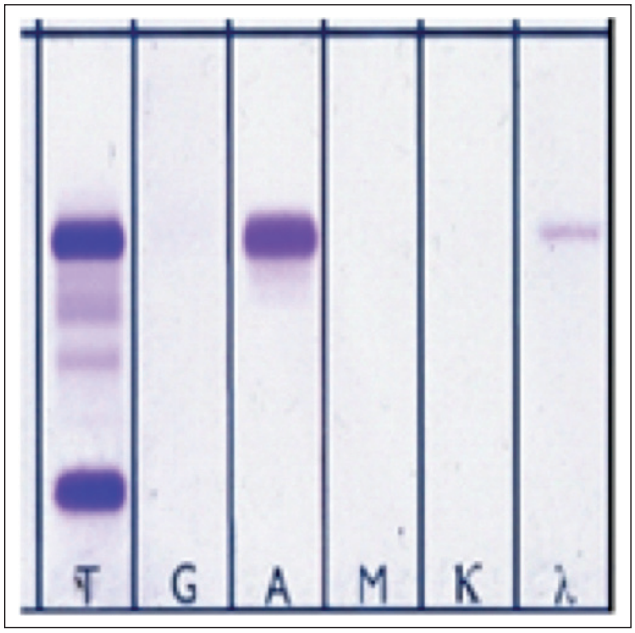



**Figure 3:** Immunoelectrophoresis by agarose gel (IFE) showed a monoclonal band of IgA heavy chain with a lambda free chain.

diagnosis of celiac disease (Marsh type 3c), which was confirmed with the laboratory investigations (Table 1).

Since the serum total protein level was remarkably high (Table 1), protein electrophoresis was performed to exclude any monoclonal plasma dyscrasias. A characteristic M-Protein was detected in the gamma region (Figure 2) and monoclonal IgA and lambda bands were obtained in the IFE (Figure 3), which was also confirmed by an alternative method; CZE/immunosubtraction (Figure 4). Urine immunofixation studies revealed no monoclonal heavy or free light chains. The bone marrow trephine biopsy revealed 45% atypical plasma cell infiltration with CD38 and CD138 immunophenotypes and positive for

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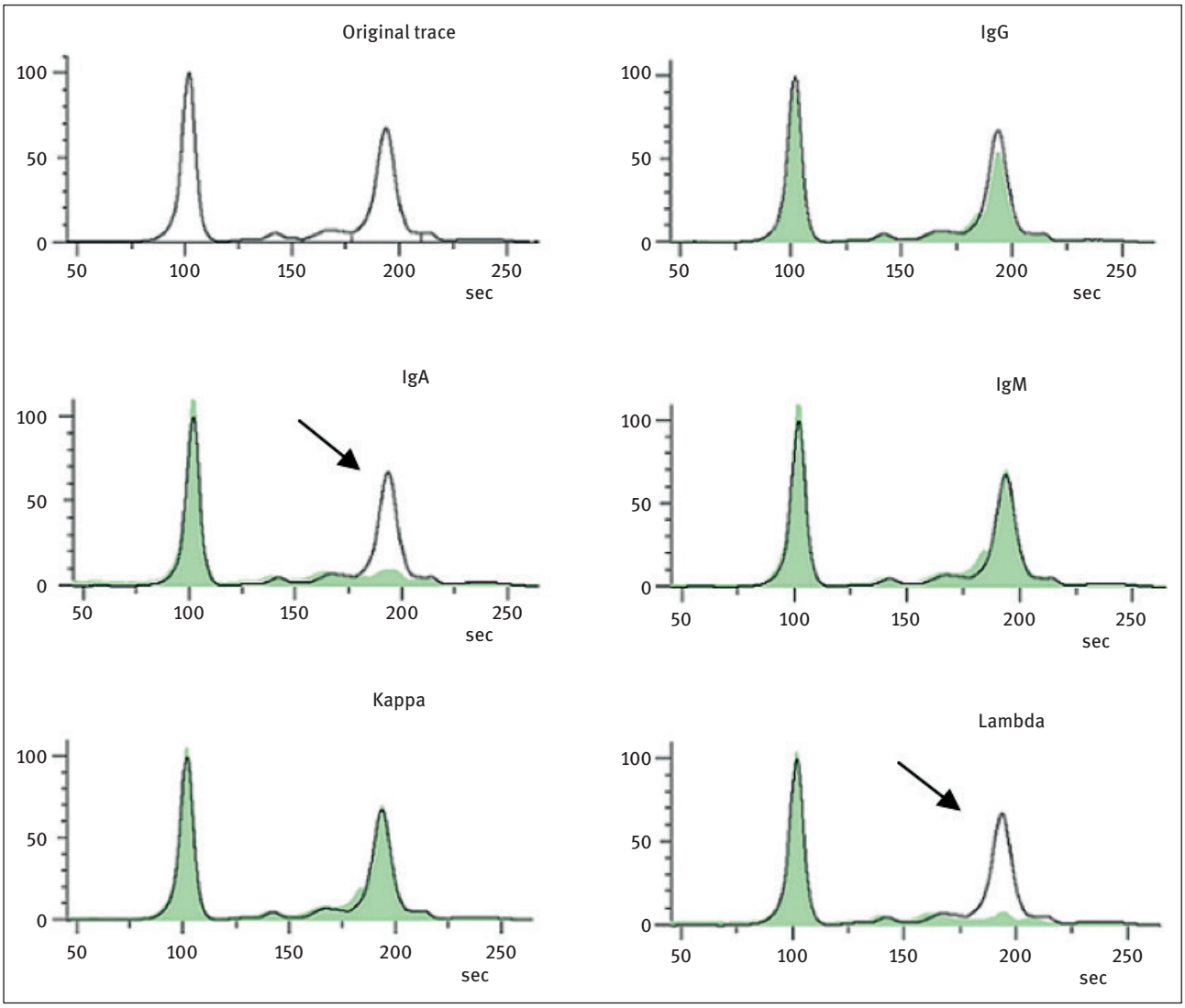



**Figure 4:** The serum immunosubtraction report using V8 automated clinical capillary electrophoresis (Helena, UK). The arrows indicate specifically subtracted parts of immunoglobulins which means those are monoclonal paraproteins. In this report, a monoclonal paraprotein is present: Ig A ʎ, report shows heavy and light chains separately. The immunosubtraction method separates serum proteins, following an incubation of serum in the presence of antisera for specific heavy and light chains, thus removing them; detection is based on their absence. The empty space shown by the arrows are the subtracted parts.

IgA and lambda immunohistochemical stains. When the patient was scanned for bone lesions, four focal lesions were determined on the humerus, Th9, Th10, and L2 vertebral corpus in the magnetic resonance imaging. The patient was diagnosed to have MM, stage IIA (Durie and Salmon staging system) and in the cytogenetic studies she was found to be negative for immunoglobulin heavy chain translocations t(11;14), t(14;16) and 17p deletions. With all these findings, the patient was put on a gluten-free diet, together with the chemotherapy schedule for MM. Genetic counselling and a CD scanning for the whole family were planned.

## 1.2 Methods used in the clinical laboratory

Biochemical studies were performed with a Dimension ExL- autoanalyzer (Siemens-Germany). Nephelometric measurements of heavy chains of immunoglobulins were performed with a BN II-nephelometer (Siemens-Germany). Total and free light chains of immunoglobulins were measured by a SPAplus® Specialist Protein Analyzer (Binding site-UK). Serum protein electrophoresis and CZE/immunosubtraction were performed by V8 automated clinical capillary electrophoresis (Helena, UK). Serum and Urine IFE was performed by using SAS-1 Agarose gel (Helena, UK).

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## 2 Discussion

CD is an autoimmune disorder with mostly nonspecific symptoms and it has been stated that only approximately 10% to 15% of the patients have been diagnosed and treated [1]. The availability of serologic testing for celiac disease and the common use of endoscopy, made it possible to identify patients who have the disease but have variable degrees of histopathologic changes and symptoms. Today CD has several categories. Asymptomatic CD with which patients have no evident malabsorption and other disease manifestations, but positive blood tests and abnormal small intestine histology. Those patients are shown to not experience new symptoms in their lifetime if they are detected and put on a gluten-free diet [2]. Potential CD, with which patients have positive celiac-specific serology with normal cellular histology and finally CD with manifestations, positive serology, and histology [6]. Symptoms of the disease appear with the ingestion of gluten and it is broken down to gliadin, which provokes antibodies towards tissue transglutaminases yielding chronic inflammatory changes such as induction of a CD 4 helper T–cell-mediated inflammatory response that activates the interferon-gamma release and CD 8-T cell. These changes cause tissue damage, intestinal mucosa inflammation, crypt hyperplasia, lymphocyte infiltration and villus atrophy. Changes in the intestinal mucosa are associated with the abnormal excretion of fat and malabsorption of vitamins and minerals [6].

In Celiac disease, lymphoproliferative disorders and intestinal tumors are the most commonly seen malignancies [3]. In this particular patient presented, although her age was young for MM, with the CD co-existence, she was diagnosed to have MM with no obvious clinical evidence. The association of CD with MM is documented in a few cases [7,8] in which the patients were approximately 65 years old. Our patient is relatively young according to the other case reports and her diagnosis of both diseases were made at nearly the same time. She had an autoimmune disease, such as CD, which might be a risk factor for the early-onset of multiple myeloma.

Renal failure can be encountered in MM patients as a result of excessive production of monoclonal proteins. In such patients precipitation of light chains within the distal and collecting tubules present as cast nephropathy. Tubulointerstitial fibrosis which is a predominant feature of myeloma kidney, develops due to activation of inflammatory cascades triggered by interaction of free light chains with proximal tubule cells [9]. To prevent life threatening renal injuries early diagnosis and intervention remains the cornerstone in MM patients. Immunotyping and immunonephelometric quantitation of heavy and light chains of immunoglobulins provide important information about the potential renal injury and prognosis [9]. Thus, cases with high monoclonal proteins, such as the present case, must be carefully monitored for potential renal damage.

Gold standard for the immonotyping of monoclonal paraproteins is IFE with agarose gel electrophoresis however the CZE/immunosubtraction method with capillary electrophoresis can be applied as an alternative technique [9]. IFE procedure involves dissemination of specific antibodies after electrophoresis and matched immunoglobulin heavy and light chains are linked and stained. However, with the development of capillary zone electrophoresis, an alternative method combined with CZE for identifying monoclonal immunoglobulins has emerged: the immunosubtraction method, also called immunotyping or immunodisplacement, separates serum proteins following the incubation of serum in the presence of antisera for heavy and light chains, thus subtracting them [9]. Detection is based on their absence when compared to the original track of serum protein electrophoresis. In CZE, the sample runs through the narrow capillary tubes and direct protein detection is performed by a measurement at 200 nm, eliminating the need for staining [9]. CZE/immunosubtraction method is easy to interpret and enables rapid and automated reporting.

The risk of multiple myeloma (MM) has been found to be associated with autoimmune diseases such as ankylosing spondylitis, autoimmune hemolytic pernicious anemia, scleroderma, Sjögren syndrome, and ulcerative colitis [10]. Hemminki *et al*. analyzed myeloma risk and survival in patients with different autoimmune disease for 17 years and found that MM increases after ankylosing spondylitis and systemic sclerosis [10]. Autoimmune diseases are characterized by the activation of T cells or B cells in the absence of foreign antigens. Auto-antigens trigger the rapid proliferation of the immune cells, which in turn creates a pro-malignant chronic inflammatory state. Myeloma arises from B-cells with somatic hypermutations in the variable region of immunoglobulin genes and long lasting chronic antigenic stimulation has been suggested to drive myeloma progression [10]. Celiac disease has one of the strongest autoimmune reactions including interferon-gamma with non-specific symptoms and both focal organ and lymphoproliferative malignancies.

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This patient is presented in light of the rarity of CD and MM associations, especially in young patients with nonspecific symptoms. Laboratory investigations indicated mild anemia that either MM or CD might have caused. MM was diagnosed by bone marrow biopsy findings, magnetic resonance scanning and is characterized by IgA-lambda monoclonality. The diagnostic criteria for MM and risk assessment for survival are well defined by the International Myeloma Working Group [4]. Renal function impairment is one of the prognostic factors, together with beta 2-microglobulin concentrations, hemoglobin concentrations, hypercalcemia, the presence of circulating plasma cells, albumin concentrations, and cytogenetic status [4]. Concerning these prognostic factors, the patient is in the low risk and high survival group. We believe that celiac disease had played a great role in the development of MM in this particular patient with an IgA monoclonality and conclude that CD patients, even if they are young, must be monitored for plasma dyscrasias. It is shown that delayed diagnosis of CD increases the risk of malignancy and is associated with a variety of malignancies [3]. Moreover, a decrease in the risk of malignancy with time after diagnosis is clearly shown, which is attributed to the adoption of a gluten-free diet [3]. Hence it is important for the patients with CD to be diagnosed early and put on a gluten-free diet in means of reducing chronic inflammation and decreasing the risk of malignancy.

**Conflict of interest:** None declared.

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