EUR. J. ONCOL.; Vol. 21, n. 3, pp. 174-179, 2016

Initial presentation of an unspecified peripheral T-cell lymphoma as inflammatory polyarthritis and hypereosinophilia

Gulsum Emel Pamuk[1], Omer Nuri Pamuk[2], Ferda Harmandar[3], Mehmet Sevki Uyanik[1], Fulya Oz Puyan[4], Nesibe Yesil[5], Oner Dogan[6]

[1] Trakya University Medical Faculty, Department of Hematology, Edirne-Turkey; [2] Trakya University Medical Faculty, Department of Rheumatology, Edirne-Turkey; [3] Antalya State Hospital, Department of Internal Medicine, Antalya-Turkey; [4] Trakya University Medical Faculty, Department of Pathology, Edirne-Turkey; [5] Ankara Numune Research and Education Hospital, Department of Rheumatology, Ankara-Turkey; [6] Istanbul University Istanbul Medical Faculty, Department of Pathology, Istanbul-Turkey

Summary. *Premise:* There may be signs of joint and bone involvement in hematologic malignancies, but it is most rare for hematologic malignancies like lymphomas to present with joint symptoms. *Patient:* A 49-year-old male patient was admitted with rheumatoid arthritis-like symmetrical polyarthritis, morning stiffness, cutaneous vasculitis and hypereosinophilia. Autoantibodies, like rheumatoid factor, anti-citrullinated cyclic peptide, antinuclear antibody, anti-nuclear cytoplasmic antibody, were negative. After 4 months of follow-up, the patient developed a diffuse cutaneous rash and multiple lymphadenopathies. Lymph node biopsy was compatible with peripheral T-cell lymphoma, unspecified. *Result:* The patient was administered, respectively, CHOP and ICE chemotherapy regimens to which he was refractory. He died from infection and respiratory failure. *Conclusion:* It should be borne in mind that T-cell lymphomas may have unusual presentations with arthritis and hypereosinophilia.

Key words: rheumatoid arthritis (RA), peripheral T-cell lymphoma-unspecified (PTCL-U), Hypereosinophilia, arthritis, lymphoma

Introduction

The frequency of hematologic malignancies, like lymphoma, is higher in patients with diseases like rheumatoid arthritis (RA) and Sjögren syndrome, especially when there is active disease (1, 2). Conversely, some patients with hematologic malignancies may develop signs like inflammatory arthritis which point to a rheumatologic disease (1-7). Nevertheless, the progression of findings like arthritis and vasculitis to lymphoma is exceedingly rare; and there are limited case reports in the literature (8, 9). There are many pathogenic mechanisms which cause bone and joint pain in lymphomas, including malignant infiltration of the bone and bone marrow (8). Nevertheless, the real coexistence of arthritis and vasculitis in lymphomas is very rare.

Here, we describe one patient who presented with inflammatory polyarthritis and cutaneous vasculitis, who had hypereosinophilia, and later developed peripheral T-cell lymphoma, unspecified (PTCL-U).

Illustration of case

A 49-year-old man presented to our hospital in January 2008 complaining of arthralgia and swelling

of the bilateral proximal interphalangeal, metacarpophalangeal, elbow, wrist, knee and ankle joints which had been present for 4 months. He talked of morning stiffness lasting for about an hour. His personal and medical history were unremarkable. The physical examination was normal, except for swelling and tenderness of the joints. Laboratory results were as follows: hemoglobin, 13.6 g/dl; leucocytes, 13400/mm^3; platelets, 450000/mm^3; erythrocyte sedimentation rate (ESR), 42 mm/hour; C-reactive protein (CRP), 1.8 mg/dl; and creatinine, 1.8 mg/dl. Urinanalysis was normal. Rheumatoid factor (RF), anti-citrullinated cyclic peptide (anti-CCP), antinuclear antibody (ANA), and antinuclear cytoplasmic antibody (ANCA) were negative. Chest and hand X-rays were normal. The patient was diagnosed as RA and started to be administered deltacortril 7.5 mg/day, methotrexate 10 mg/week, and diclofenac 150 mg/day.

The patient was readmitted into our rheumatology department two months later still complaining of symmetrical polyarthritis and morning stiffness. He admitted to not having taken his medication regularly. On physical examination, he had arthritis, and cutaneous rashes over the pretibial regions and dorsa of his feet. Laboratory data were as follows: hemoglobin, 13.4 g/dl; leucocytes, 17800/mm^3; platelets, 460000/mm^3; total protein, 6.1 g/dl; albumin, 2.9 g/dl; LDH, 247 U/L (Normal<192 U/L); ESR, 37 mm/hour; CRP, 1.4 mg/dl. The absolute numbers of leucocyte subsets in peripheral blood smear were: neutrophils, 6500/mm^3; lymphocytes, 3900/mm^3; monocytes, 1200/mm^3; and eosinophils, 6200/mm^3. RF, anti-CCP, ANA, p-ANCA, c-ANCA, and hepatitis B and C serologies were negative. The bcr-abl gene transcript and JAK2-V616F mutation were negative with PCR. He also tested negative for PDGFR-α and PDGFR-β mutations. The stool cultures tested negative for parasites three times. Immunoglobulin E level was 1266 IU/ml (Normal <100 IU/ml). Skin biopsy findings were compatible with leucocytoclastic vasculitis. Bone marrow aspiration showed the presence of 20% normal-appearing eosinophils. The bone marrow biopsy confirmed the increase in eosinophils. Computed tomographies (CT) of the thorax and abdominopelvic cavity were normal. The patient was administered low-dose steroids and diclofenac.

Four months after initial presentation, the patient was admitted with cervical swelling, and itchy and generally erythematous lesions over his skin. On physical examination, he had bilateral cervical lymphadenopathy, hepatosplenomegaly, and most of his skin surface was erythematous. He had no arthritis. Laboratory data revealed: leucocytes, 26100/mm^3 (leucocyte formula showed neutrophils, 12700/mm^3; lymphocytes, 6100/mm^3; monocytes, 3100/mm^3; and eosinophils, 4200/mm^3); total protein, 5.4 g/dl; albumin, 2.3 g/dl; LDH, 295 U/L; ESR, 14 mm/hour; CRP, 1.65 mg/dl. One week after hospitalization, he developed bilateral axillary and inguinal lymphadenopathies. Thorax CT showed lymph nodes in precarinal and aortopulmonary areas; abdominopelvic CT revealed splenomegaly. Cervical lymph node biopsy revealed a diffuse infiltration of intermediate-sized atypical lymphocytes with a sclerotic stroma occupying the normal lymphoid structure. Immunohistochemical studies revealed diffuse and strong positivity for CD3, CD2, CD7, CD45RO, CD8 on the lymphoid cells. CD4 positivity was focal. CD30 and Ki-67 proliferative index was positive on 20-30% of the neoplastic cells. Cytotoxic granules of the T-cell lineage such as granzyme and perforin expression amounted to only 10%; whereas CD56, a sensitive marker for NK cells, was seen on only 1% of the lymphocytes (Figures 1, 2, 3a, 3b). Immunohistochemical findings of neoplastic cells were consistent with a T-cell lineage of cytotoxic type. The skin biopsy showed infiltration with similar cells (Figure 3c, 3d).

The patient was diagnosed with peripheral T-cell lymphoma, unspecified (PTCL-U); a CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) chemotherapy protocol was administered three times at two-week intervals with granulocyte colony stimulating factor support. He proved refractory to this chemotherapy regimen, so we switched to an ICE (ifosfamide, carboplatin, etoposide) protocol. He was given 2 courses of ICE regimen. He developed fever and dyspnea after the second ICE. Chest X-ray revealed bilateral pneumonic consolidations in both lung fields. He was started on imipenem and trimethoprim-sulfomethoxazole, but died within 24 hours.

Discussion

At initial presentation, our patient had inflammatory polyarthritis, cutaneous vasculitis, and hypereosinophilia; he developed PTCL-U 8 months after the onset of arthritis. Despite the coexistence of bone and joint involvement in lymphomas, the presence of true arthritis, presentation with arthritis, and a duration of longer than 6 months between arthritis and development of lymphoma are quite rare (8). Our patient was first treated as a case of inflammatory arthritis, that is RA; after 4 months he developed signs of lymphoma with skin involvement. Thus final diagnosis was delayed. Although his initial symptoms fulfilled the criteria for RA, antibodies like RF, anti-CCP were negative and there were no erosive lesions on a hand X-ray. One of the most noteworthy features in our case was the 8-month period between the initial arthritic symptoms and diagnosis of lymphoma. It is known that the risk for the development of lymphomas is higher in RA patients, especially in those with severe deforming disease. Nevertheless, our patient developed lymphoma only 8 months after arthritis and vasculitis and this can be considered as a short period which does not support the possibility of a chronic inflammation-induced tumorigenesis.

The arthritis accompanying lymphomas is generally in the form of symmetrical, nonerosive, nondeforming polyarthritis (8). Generally the small joints of the hand are involved, as in RA, and in the absence of other

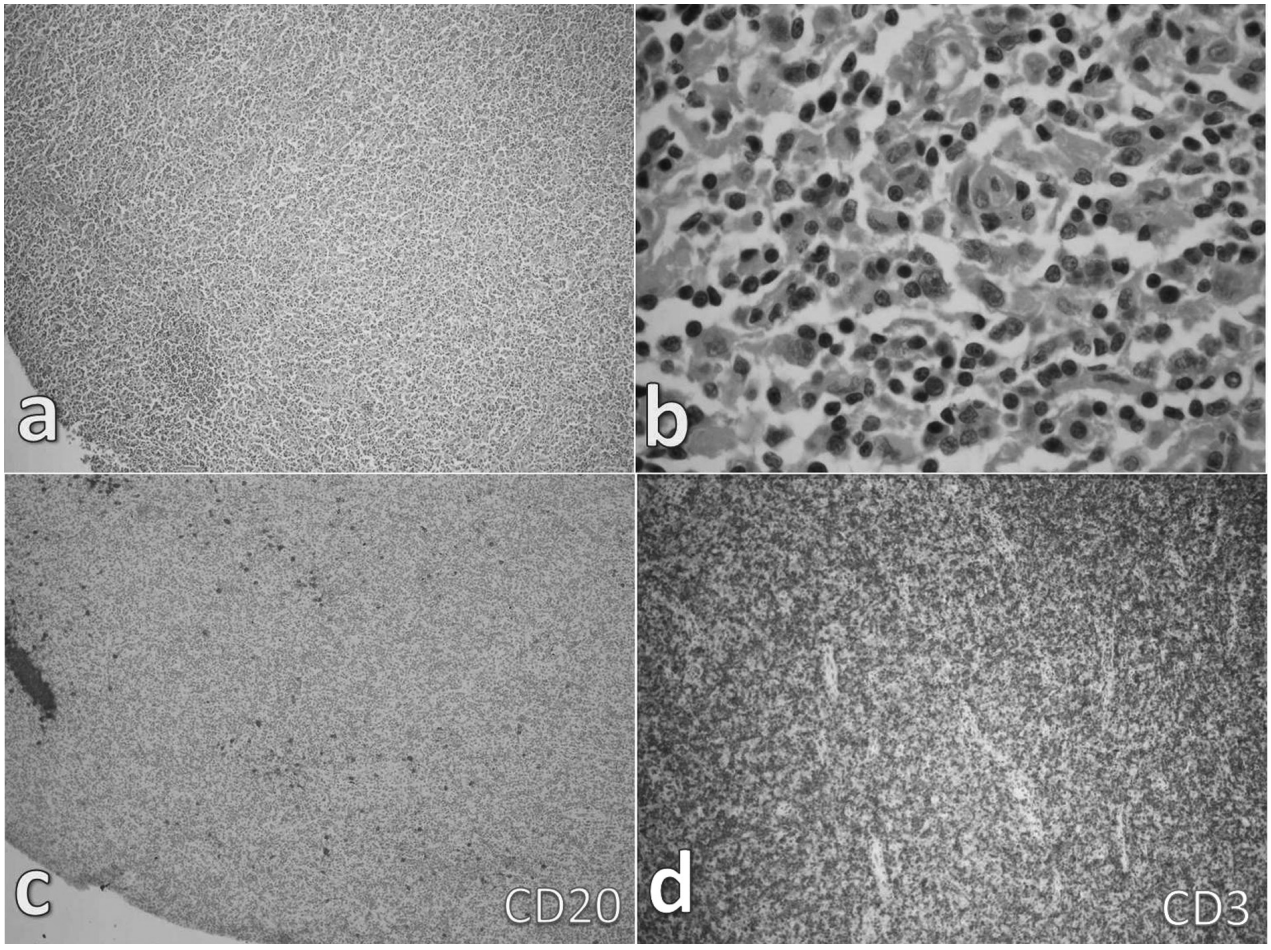

Figure 1. a) Lymphoid infiltrate consists of a diffuse infiltration of medium-sized monotonous lymphoid cells (H&E x 20). b) High-power view shows polymorphic infiltration with small and large cells, admixed with histiocytes (H&E x 40). c) Loss of CD20 staining due to lymphoid infiltration in the lymph node (IHC x 10). d) CD3 immunopositivity of the neoplastic cells (IHC x 10).

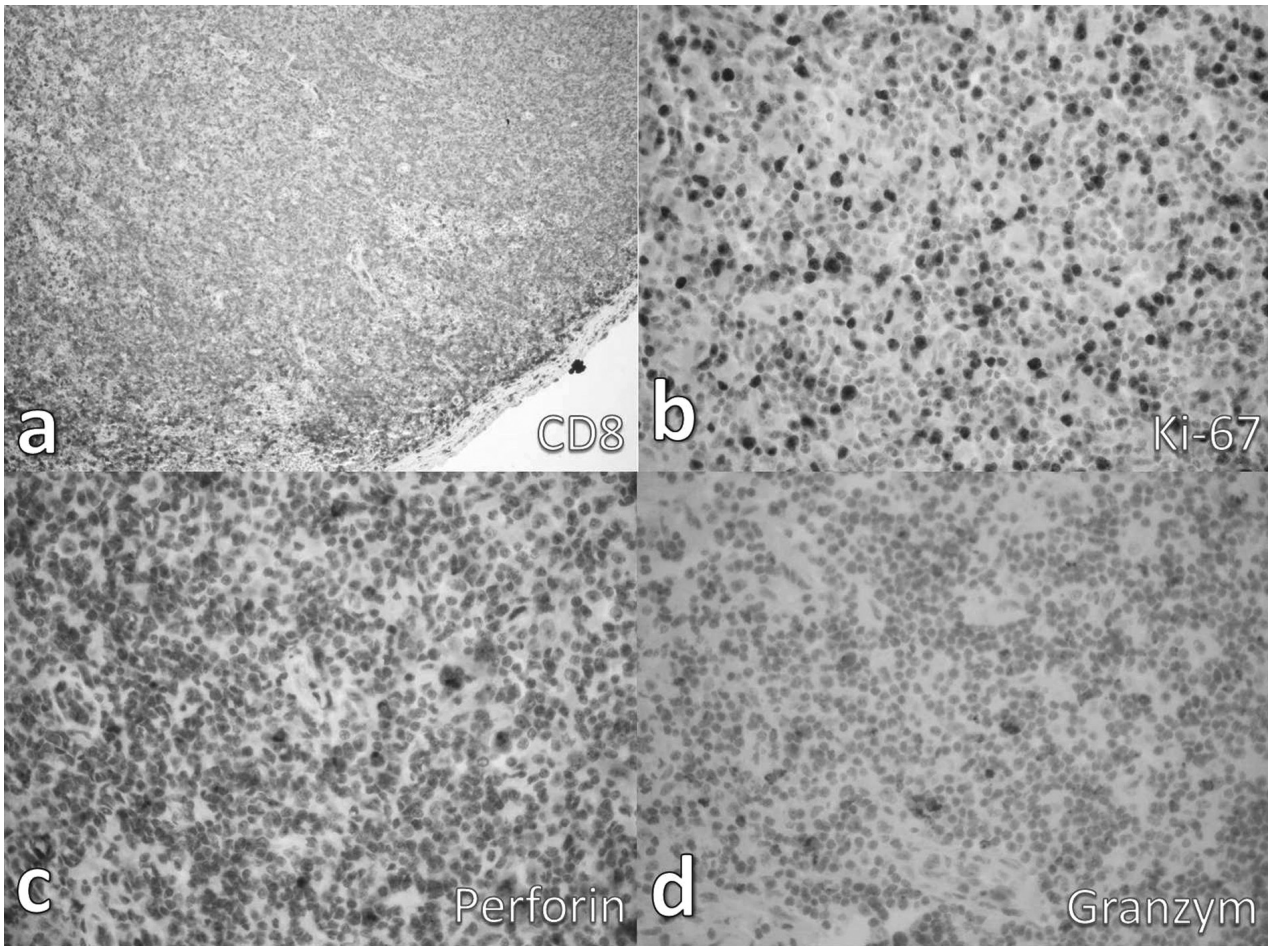

Figure 2. a) Diffuse strong CD8 immunopositivity (IHC x 10). b) Ki-67 proliferation index is around 30% (IHC x 20). c) Focal positivity for perforin (IHC x 20). d) Focal positivity for granzyme (IHC x 20).

clinical features of lymphoma, it might not be possible to distinguish this from RA. Our patient was initially treated as RA but RA-related antibodies were negative. In some lymphoma subtypes, some autoantibodies might be detected in patients with arthritis (8); however, RF and ANA are usually negative in these patients.

Although various different mechanisms have been suggested, the exact pathogenesis of arthritis in lymphomas remains unknown. The invasion of the lymphoma into the joint is theoretically possible; however, the occurrence of arthritis with immune mechanisms is more probable. The immune disorders in lymphoma are differentiation of T cell responses, overexpression of cytokines like tumor necrosis factor alpha (TNF-α), interleukin-1 (IL-1), and IL-6 (8). It is also known that the frequency of lymphoma is increased in diseases like Sjögren, RA, and SLE; and that using cytotoxic drugs for these diseases also increases the risk (10). Our patient did not have a history of any other disease or cytotoxic drug intake.

In addition to arthritis, our patient also had signs of hypereosinophilia. Presentation of T-cell lymphomas with eosinophilia has rarely been reported in the literature (11). Reactive eosinophilia is thought to be induced by cytokines and chemokines produced by benign or neoplastic T helper cells (12). It has been stated that T cells secrete IL-4 and IL-13 which are responsible for the increased IgE level and hypereosin-

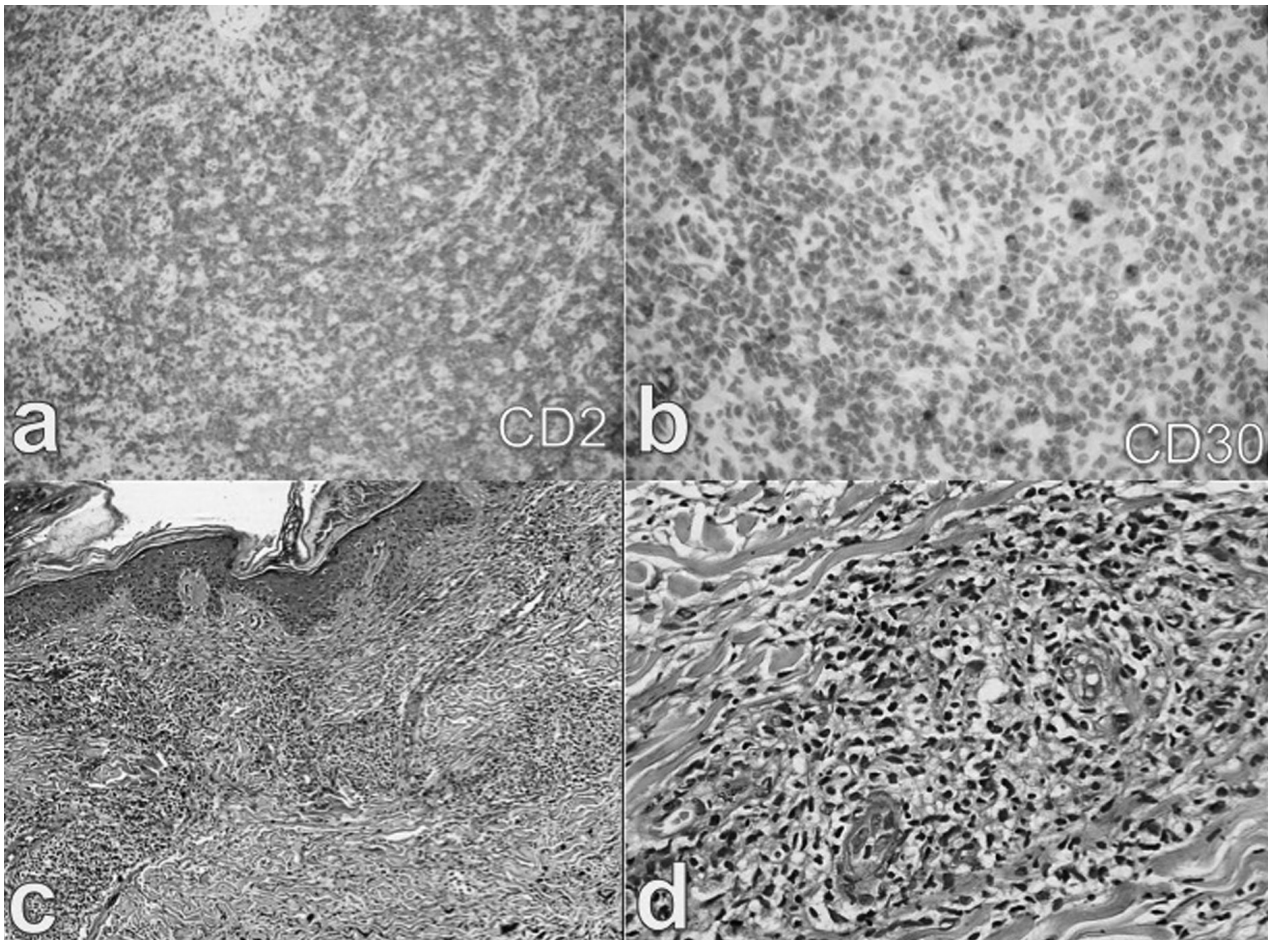

Figure 3. a) Diffuse strong CD2 immunopositivity on the neoplastic cells (IHC x 10). b) CD30 immunoexpression on some of the neoplastic cells (IHC x 20). c-d.Skin biopsy with dermal perivascular atypical lymphoid infiltration (c.H&E x 10, d.H&E x 20).

ophilia (13). We assume that our patient's T-cell functions were initially impaired and tolerance was broken; autoimmune features, like arthritis and vasculitis, developed secondarily to the increase in eosinophils, and signs of classic lymphoma developed thereafter. Nevertheless, it is difficult to comment on why the course in our patient was quite different from others.

Our patient initially had biopsy-proven vasculitic skin lesions on his lower extremities. He later developed skin infiltration with lymphoma. Vasculitis and related skin lesions might develop in hematologic malignancies. We administered CHOP and ICE chemotherapy regimens; however, the patient was refractory and died of pneumonia. His initial arthritic symptoms were able to be controlled with low-dose steroids.

Conclusions

T-cell lymphomas might rarely present with arthritis, vasculitis, and hypereosinophilia. The differentiating features from RA are the absence of erosions on hand X-ray, negativity for autoantibodies like RF, and anti-CCP in the presence of symptoms reminiscent of RA. Today, RA is diagnosed earlier than before and it is recommended to start disease-modifying anti-rheumatic drugs earlier in the disease course. Hence, in the presence of unexpected blood counts, like hypereosinophilia, the diagnosis of RA should be questioned. As a result, it should not be forgotten that immune activation and differentiation into lymphoma might result from (?) an autoimmune disease presentation.

References

1. Boumpas DT, Wheby MS, Jaffe ES, *et al.* Synovitis in angioimmunoblastic lymphadenopathy with dysproteinemia simulating rheumatoid arthritis. Arthritis Rheum 1990; 33: 578-82.
2. Davies PG, Fordham JN. Arthritis and angioimmunoblastic lymphadenopathy. Ann Rheum Dis 1983; 42: 516-8.
3. Gravallese EM, Winalski CS, Longtine J, *et al.* Polyarthritis in a 78-year-old woman. Arthritis Rheum 1994; 37: 1087-95.
4. Layton MA, Musgrove C, Dawes PT. Polyarthritis, rash, and lymphadenopathy: case reports of two patients with angioimmunoblastic lymphadenopathy presenting to a rheumatology clinic. Clin Rheumatology 1998; 17: 148-51.
5. McHugh NJ, Campbell GJ, Landreth JJ, *et al.* Polyarthritis and angioimmunoblastic lymphadenopathy. Ann Rheum Dis 1987; 46: 555-8.
6. Raskin RJ, Tesar JT, Lawless OJ. Polyarthritis in immunoblastic lymphadenopathy. Arthritis Rheum 1982; 25: 1481-5.
7. Rothwell RS, Mant MJ, Davis P. Angioimmunoblastic lymphadenopathy associated with polyarthritis. Ann Rheum Dis 1980; 39: 406-9.
8. Tsochatzis E, Vassilopoulos D, Deutsch M, *et al.* Angioimmunoblastic T-cell lymphoma associated arthritis: case report and literature review. J Clin Rheumatol 2005; 11: 326-8.
9. Falcini F, Bardare M, Cimaz R, *et al.* Arthritis as a presenting feature of non-Hodgkin's lymphoma. Arch Dis Child 1998; 78: 367-70.
10. Stroehmann A, Dörner T, Lukowsky A, *et al.* Cutaneous T cell lymphoma in a patient with primary biliary cirrhosis and secondary Sjögren's syndrome. J Rheumatol 2002; 29: 1326-9.
11. Scales JW, McMichael A. Persistent peripheral eosinophilia and cutaneous non-Hodgkin's lymphoma: a case report and review of the literature. Cutis 2001; 67: 67-70.
12. Helbig G, Stella-Holowiecka B, Bober G, *et al.* The achievement of complete molecular remission after autologous stem cell transplantation for T-cell lymphoma with associated hypereosinophilia, rare aberration t(6;11) and elevated IL-4 and IgE. Haematologica 2006; 91 (8 Suppl): ECR42.
13. Hovenga S, de Graaf H, Joosten P, et al. Enteropathy-associated T-cell lymphoma presenting with eosinophilia. Neth J Med 2003; 61: 25-7.

Received: 2.5.2014
Accepted: 15.7.2016
Address: Prof. Dr. Gulsum Emel Pamuk
Eski Yildiz Cad. Park Apt. No:22 Daire: 18,
34349, Besiktas, Istanbul, Turkey
Tel. +90 284 2369796
E-mail: gepamuk@gmail.com