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# LETTERS AND CORRESPONDENCE

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## Unusual Behavior of Primary Tonsillary Lymphoma

*To the Editor:* Primary tonsillary lymphoma accounts for less than 1% of head and neck malignancies. Tonsillectomy is used to mainly establish the diagnosis and can be performed for localized small lesions. In general, the patients are treated by chemotherapy and/or radiotherapy [1,2].

We present a 23-year-old woman who was referred to our ENT clinic with asymmetric tonsillary enlargement and acute bleeding. Tonsillectomy was performed. In paraffin sections; a tumor composed of large lymphoid cells that were positive for CD20, bcl-2, and p53 by immunohistochemistry was identified. Ki-67 index was roughly 80% (Figure 1). Polymerase chain reaction for immunoglobulin gene rearrangements was performed using DNA extracted from paraffin-embedded tissue and showed a single band indicating the presence of a clonal B cell proliferation. A diagnosis of "Diffuse Large B Cell Lymphoma" was rendered. No clinical or radiological evidence for tumor involvement in any other site was identified and the patient was accepted as Stage I clinically. The patient did not accept any further treatment. The patient was followed periodically every 6 months. Recurrence or systemic involvement was not observed during the 5-year-follow-up.

This case is unusual since only tonsillectomy was curative. In general, radiation therapy is considered the primary mode of therapy for localized disease in tonsil lymphomas (stages I and II) [3,4]. In one study, Jelic et al. reported a cure rate of 80% among their stage I NHL patients, who they followed without any therapy. In light of their experience as well as our observation, therapy options for localized NHL cases should be re-evaluated.

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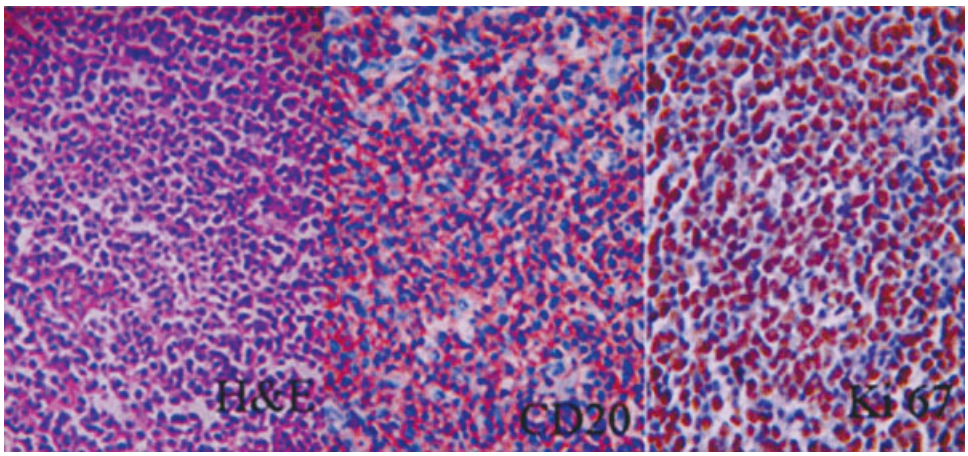


**Fig. 1. Tonsillary large B cell lymphoma (H&E ×200, immunoperoxidase CD20 ×400, Ki67 ×400). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]**

5. Jelic S, Frim O, Gligorijevic G, Gavrilovic D, Manojlovic N, Jovanovic V, Opric M. A controversial issue: could a watch-and-wait policy for patients with non-Hodgkins lymphoma clinical stage I or IE with no lymphoma left following diagnostic surgery be justified? Results of a single centre study. Hematol Oncol 1997;15:53–61.

## Variability of ZAP 70 Expression in a Patient with CLL

*To the Editor:* A previously healthy 64-year-old male presented in January 2002 with atypical chest pain. He was found to have a white blood cell count of 40.6 $\times$ $10^9$/L with 76% lymphocytes. Physical examination was normal with no lymphadenopathy or splenomegaly. The metabolic profile was normal. The peripheral smear showed a preponderance of mature lymphocytes and smudge cells. There were no previous complete blood counts for comparison. Peripheral blood flow cytometry confirmed our clinical diagnosis of chronic lymphocytic leukemia, with a typical expression of CD5, CD20, and CD23. His stage was Rai 0. We recommended observation. The patient continued to follow up in our clinic without a change in his clinical condition or laboratory data. In early 2004, ZAP 70 testing by flow cytometry became available at our institution and was performed on this patient. Fifteen percent of the tumor cells expressed ZAP 70, suggesting a favorable prognosis. CD38 was 4%. One year later, the patient developed a rapid doubling of the lymphocyte count reaching up to 288 $\times$ $10^9$/L. This was complicated by a sudden loss of vision in his right eye and evidence of spontaneous tumor lysis. Physical examination revealed a palpable spleen tip and minimal axillary and cervical lymphadenopathy. His hemoglobin and platelet count were 9.0 g/dl and 107 $\times$ $10^9$/L, respectively. He had evolved to Rai stage III. Bone marrow aspirate and biopsy revealed hypercellularity with 50% involvement by CLL. At this time, ZAP 70 was expressed by 91% of the tumor cells within the bone marrow and CD38 by 25%. Cytogenetic analysis revealed deletion 11q and deletion 13q. Peripheral blood flow cytometry was repeated and revealed a ZAP 70 similar to the bone marrow results. The patient was started on therapy with a fludarabine-based regimen and is tolerating this therapy well.

Over the past few years, there have been significant advances in the understanding of biologic markers and predictors of disease outcome in CLL [1]. One of these predictors is the $\zeta$-chain-associated protein kinase 70 (ZAP 70). The expression of ZAP 70 is reported to correlate with $IgV_H$ mutational status, disease progression, and survival. In addition, this expression does not seem to change over time [2]. Rassenti et al. reported that although ZAP 70 expression was strongly associated with the presence of the unmutated $IgV_H$ gene, ZAP 70 was a stronger predictor of the need for treatment in B-cell CLL [3].

We hereby report an observation of a change in ZAP 70 expression associated with disease progression in a patient with CLL. Clinicians should be aware that variability in ZAP 70 expression is possible, especially when it does not correlate with clinical behavior.

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## Efficiency of Rituximab in the Treatment of Autoimmune Thrombocytopenic Purpura Associated with Common Variable Immunodeficiency

*To the Editor:* In 1994 a 10-year-old girl was diagnosed with common variable immunodeficiency. One year later, she presented with sarcoidosis and was treated with steroid therapy (dosage: 1 mg/kg) but ocular and pulmonary relapses occurred 10 months later during dose tapering. Immunosuppression with azathioprine and then methotrexate was able to induce a remission 9 months after the onset. During the next 3 years, relapses with eye, medullar, and brain involvement occurred, which responded to steroid treatment alone. Long-term monthly intravenous immunoglobulin was then prescribed for prevention of recurrent bacterial infections. She presented with unusual metrorrhagia in September 2003.

A blood cell count showed 14 $\times$ $10^9$/L platelets and 0.3 $\times$ $10^9$/L neutrophils. Bone marrow smear and biopsy showed megakaryocytic hyperplasia and normal erythroid cells, which were consistent with a peripheral consumptive process. No granulomas and no lymphoproliferative process were found in the biopsy. Steroid therapy (1 mg/kg) and intravenous immunoglobulin were inefficient. Vincristine at the dose of 2 mg every 15 days caused intolerable peripheral neuropathy after three courses without any platelet count improvement. Rituximab at 375 mg/m$^2$ days 1, 8, 15, and 21 was started. Platelet count reached 30 $\times$ $10^9$/L 3 weeks later and was stabilized at 130 $\times$ $10^9$/L 12 months later. Steroid tapering to 10 mg/day has been possible under rituximab, and the patient resumed her normal life. Neutrophils were normalized.

Common variable immunodeficiency (CVID), the most frequent congenital immunodeficiency after IgA deficiency, is characterized by a primary deficiency in at least two isotypes of $\gamma$-globulins and recurrent bacterial infections. The prevalence has been estimated at 1 in 30,000 to 50,000 individuals. It may be associated with autoimmune diseases or manifestations, chronic inflammatory diseases, malignancy, or sarcoidosis-like disease. The most frequent autoimmune disorder in primary immune deficiencies is immune thrombocytopenic purpura (ITP) in 7.6% of patients, followed by autoimmune hemolytic anemia (AIHA) in 4.8% [1]. Autoimmune manifestations are present in about 20% of patients with immunodeficiency. Michel et al. reported that 14 patients of 27 (63%) with ITP and CVID achieved a lasting, complete response with steroids with or without intravenous immunoglobulin (IV-Ig). IV-Ig therapy alone did not seem effective. Other therapies have been used (danazol, aziathioprine, or cyclophosphamide) with some toxicity [2]. Splenectomy, performed in 30 patients of 498 with CVID, was associated with serious complications: 3 patients died from pneumococcemia soon after splenectomy, and 5 had severe postoperative infections [3] [4].

Anti CD20 chimeric monoclonal antibody (rituximab) is targeted at activated B-lymphocytes and therefore decreases the production of pathological autoimmune antibodies. This molecule has been used successfully in the treatment of B-cell lymphomas and autoantibody-mediated diseases such as rheumatoid arthritis, lupus erythematosus, AIHA, and ITP. Anti-CD20 monoclonal antibody was used to treat AIHA associated with CVID [5] in one case. Rituximab may be more efficient than classical immunosuppressive therapy in the treatment of ITP associated with CVID. It may prove an efficient and safe alternative to splenectomy.

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## Simultaneous Development of Philadelphia Chromosome-Positive and -Negative Leukemias in the Same Patient

*To the Editor:* This 67-year-old woman was referred for a white blood cell (WBC) count of 220 $\times$ $10^9$/L, neutrophilia, left shift, and the presence of the Philadelphia chromosome (Ph) in 40% of peripheral blood cells (54/136 cells) by FISH (fluoresence in situ hybridization) (bcr:abl dual color translocation probe, Vysis Inc., Abbott Laboratories). Cytogenetics were not performed. She was diagnosed with chronic phase chronic myelogenous leukemia (CML) and was prescribed 1 g hydroxyurea (HU) daily and allopurinol 1 month prior to visiting our clinic. One week prior to the visit, the HU was decreased to 500 mg daily when the WBC decreased to 28 $\times$ $10^9$/L and platelets to 74,000 $\times$ $10^9$/L. When we first saw her, the patient reported feeling unwell for 10 months. She had recently developed night sweats, fever, and dyspnea and was tachypneic and hypoxic. Physical examination revealed poor lung ventilation and an enlarged spleen and liver. CBC and differential were as follows: Hgb 82 g/L, WBC 205.8 $\times$ $10^9$/L, platelets 261 $\times$ $10^9$/L; blasts 2%; promyelocytes 2%; myelocytes 4%; metamyelocytes 15%; stabs 10%; neutrophils 38%; lymphocytes 18%; monocytes 10%. The patient was admitted. She developed acute respiratory distress syndrome(ARDS) and was intubated and ventilated. HU was administered through a nasogastric tube, and the WBC decreased to 76.4 $\times$ $10^9$/L and platelets to 40 $\times$ $10^9$/L. Within 2 days the patient was extubated and the bilateral lung infiltrates cleared. A bone marrow aspirate was performed, 400 mg imatinib daily was initiated, HU held, and the patient was discharged.

Unexpectedly, the bone marrow analysis showed 23% of nucleated cells to be monoblasts, with dysplastic erythropoiesis. After 4 days of imatinib, the patient's WBC rose to 200 $\times$ $10^9$/L and platelets decreased to 14 $\times$ $10^9$/L, with 2% blasts in the peripheral blood. The cytogenetics revealed a normal female karyotype in a sample of 50 metaphases. By FISH, 8/306 (2.6%) cells contained the Philadelphia chromosome (normal value $\leq$ 2%). This low level of FISH positivity was confirmed by a quantitative PCR assay, which demonstrated $1/10^4$ bcr/abl positive cells. By immunophenotyping, the blasts coexpressed CD34, HLA-DR, CD33, and CD11c. In retrospect, the ARDS was likely due to the monoblastic leukemia.

Based on the decrease in FISH positivity for the Ph chromosome and the low level of bcr/abl transcript by quantitative RT-PCR, this patient either had chronic phase CML that transformed into a Ph− acute myeloid leukemia or two coexisting leukemias, CML and an evolving clonally unrelated leukemia. We favor the latter because the Ph chromosome is known to drive the leukemic transformation in patients who evolve to blast crisis [1]. There are case reports of secondary cytogenetic abnormalities and secondary, Ph− leukemia in patients with CML treated with imatinib [2,3], busulfan, and interferon [4,5]. In this case two leukemic processes presented synchronously and prior to treatment with imatinib.

Although deriving from a single case, the simultaneous coexistence of CML and another leukemia gives testimony to the multiclonal transformation process that sometimes develops in the bone marrow of leukemic patients. This case also illustrates the utility of FISH, quantitative PCR, and cytogenetics in the differentiation of CML from other leukemic disorders.

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## Mediterranean Spotted Fever: Presentation with Pancytopenia

*To the Editor:* Mediterranean spotted fever (MSF), Boutonneuse fever, is a tick-borne disease caused by *Rickettsia conorii* and is endemic in the Mediterranean region [1]. Although MSF is usually a benign infectious disease, unusual manifestations that have been mainly reported in severe forms, typically among elderly patients or those with underlying diseases, complicate the diagnosis [2].

A 39-year-old woman, a resident of Bursa, Turkey, was admitted with a 5-day history of fever, headache, and malaise and a 3-day history of rash. Physical examination showed fever and maculopapular rash involving the trunk, extremities, palms, and soles. Hematological findings were as follows: Hb 10.8 g/dL, WBC 1.7 $\times$ $10^9$/L with 62% polymorphonuclear cells; 9% bands; 20% lymphocytes; 6% metamyelocytes; 3% myelocytes; and platelet count 46.8 $\times$ $10^9$/L. Laboratory studies revealed an elevated CRP (13 mg/L), accelerated ESR (60 mm/h), hypoalbuminemia (2.5 mg/L), and slightly elevated serum aspartate aminotransferase (53 UI/L) and lactate dehydrogenase (386 UI/L). Bone marrow smear showed hypercellular marrow with activation of myeloid cells. After 3 days of hospitalization, we learned that she has a dog in her yard. A ''tache noire,'' the typical eschar at the site of the tick bite, was observed on the right inguinal region with more elaborate physical examination. Treatment with doxycycline (200 mg/day) was started. Resolution of fever and normalization of hematological findings were observed on the 4th and the 6th days of treatment, respectively (Figure 1).

MSF is still an endemic disease in the Mediterranean region, with the peak incidence during the summer season. The onset of MSF is sudden and

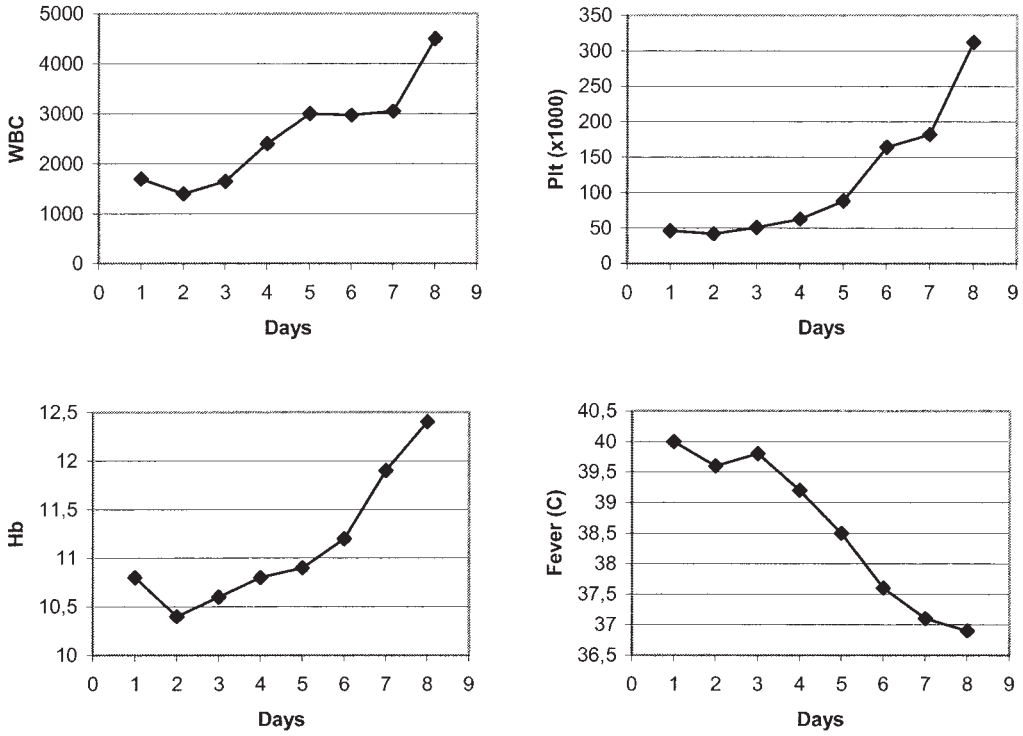


**Fig. 1. Characteristics of the patient.**

typical cases present with high fever, myalgia, headache, myositis, a black eschar (tache noire) at the tick bite site, and a maculopapular rash [3]. Although it has a benign course, severe forms can cause death, mainly in high-risk groups (e.g., the elderly or those with cirrhosis, chronic alcoholism, and glucose-6-phosphate dehydrogenase deficiency) [2]. In a recent study carried out by Anton et al. [3], leucopenia, anemia, and thrombocytopenia were observed in 23, 4, and 17% of cases, respectively. However, 36 of 144 patients had underlying diseases at baseline. Our case is interesting because she was complicated with pancytopenia without any underlying disease, and this is the first case of pancytopenia associated with MSF that we have seen.

Indirect immunofluorescence for the detection of IgM and IgG antibodies to *R. conorii* is considered the best test of choice for serologic diagnosis [4]. We did not think it necessary to make serological confirmation of MSF. Our patient displays most of the classical symptoms of MSF, especially the tache noire, which is of high diagnostic value, and the infection appeared during the summer. The impressive clinical and laboratory improvement of the patient following the administration of doxycycline also supports the diagnosis.

In conclusion, MSF should be considered a cause of pancytopenia in a patient with fever and rash who lives in or traveled to an endemic area. Finally, because in recent years a number of spotted fever rickettsias have been described in Europe, tick-borne disease should be considered a severe problem.

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