

LETTERS AND
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Rituximab-Induced Serum Sickness

To the Editor: Rituximab, a chimeric murine-human monoclonal anti CD20 antibody, is approved for the treatment of relapsed or refractory, CD20(+) B-cell, low-grade or follicular non-Hodgkin's lymphoma (NHL). This antibody is also being used and evaluated against other CD20-expressing hematological malignancies and autoimmune disorders [1]. Recently, D'Arcy and Mannick [2] reported the first case of serum sickness occurring 10 days after the patient started a protocol of 4 weekly infusions of rituximab for refractory autoimmune polyneuropathy. The patient presented with fever, polyarthritis, and transient decrease of C3 and C4 levels. IgG antibodies directed to the murine Fab' fragments of the rituximab were found [2]. We observed a similar clinical presentation in a 48-year-old woman with refractory immune thrombocytopenia (anti-nuclear factor negative). Six days after the second course of rituximab on a weekly protocol, the patient was admitted because of fever (38.5°C), malaise, symmetric polyarthritis of large and small joints, and a morbilliform skin eruption. At the same time, her platelet count dropped to 2,000, and she was treated with methylprednisolone 500 mg (i.v.) for 2 days. The patient responded favorably to the treatment, and less than 48 h after the treatment was started the symptoms and the signs of serum sickness resolved.

Although rituximab is a chimeric murine-human antibody, only 3 patients out of more than 300 patients who were treated with rituximab and were tested for human anti-chimeric antibodies showed detectable antibodies levels [3]. None of them was reported to develop serum sickness. This is the second case reported of rituximab-induced serum sickness; both cases occurred a few days after the second course of rituximab for an autoimmune disorder, and both of them responded favorably to glucocorticoid treatment. We believe that with increasing clinical experience with rituximab more cases of serum sickness will occur; therefore, the clinicians should be aware of this adverse effect.

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Effective Treatment With Recombinant Factor VIIa of Severe Bleeding Due to Acquired Factor VIII Inhibitor and Acquired Thrombocytopenia

To the Editor: Acquired hemophilia is a rare, severe hemorrhagic diathesis in nonhemophilic patients [1]. Moreover, the appearance of a coagulation factor VIII inhibitor and alteration in the platelet function are exceptional. Activated recombinant factor VII (rVIIa) has been used recently in the antihemorrhagic treatment of patients with factor VIII inhibitors and thrombopathies [2]. We present, to the best of our knowledge, the first case of a nonhemophilic patient, with acquired hemophilia and thrombopathy secondary to a malignant hemopathy, who was treated satisfactorily with rVIIa.

A 65-year-old nonhemophilic man presented a large hematoma of his right arm following extraction for arterial gasometry test. The activated partial thromboplastin time was 118 sec (control 25–40 sec), which was not corrected by normal fresh plasma; factor VIII:C 3%; factor VIII inhibitor 21 Bethesda units. White blood cell count $41.3 \times 10^9/L$ (13% monocytes, 9% bands, 8% metamyelocytes, 3% myelocytes, 2% blast cells). Bone marrow aspirate and surface immunophenotype showed characteristics of chronic myelomonocytic leukemia. Platelet aggregation showed a diminished response to ADP and collagen.

The patient had five hemorrhagic episodes (Table I). The first hemorrhagic episode was not treated because diagnosis had not been made. In addition, rVIIa was administered to the patient for surgical drainage of an abscess of his left elbow. Immunosuppressive treatment was commenced with oral cyclophosphamide (2 mg/kg/day \times 38 weeks) and oral prednisone (1 mg/kg/day \times 12 weeks). Endovenous immunoglobulins (0.4 mg/kg/day \times 5 days) were started. The inhibitor titers did not decrease. Immunosuppressive treatment was discontinued, and mercaptopurine was started, which satisfactorily returned the factor VIII level to normal so that the bleeding ceased. Twenty months later, the patient had severe pancytopenia and his general condition had worsened. At that point, inhibitor against factor VIII was detected. The patient died 4 months later of pneumonia. Acquired factor VIII inhibitors in nonhemophilic patients are very rare. Most patients have severe hemorrhages, usually during the first weeks following diagnosis, and the mortality is high. The therapeutic objective in acquired hemophilia is to eradicate the inhibitor and control the hemor-

TABLE I. Episode Characteristics; rVIIa Treatment Protocol

Episode	Date	Hemorrhage sites	Dosage	Injections	Total rVIIa (kUI)
1 st	September 1998	Soft tissue of the entire right arm (after extraction for arterial gasometry)	0	0	0
2 nd	September 1998	Right gluteus muscles	90 µg/kg/4 hr × 4 days	26	8.640
3 rd	October 1998	Soft tissue of the entire left arm (due to loss of venous access)	128 µg/kg/3 hr × 3 days 90 µg/kg/3 hr × 2 days 90 µg/kg/4 hr × 2 days	49	20.280
4 th	November 1998	Left gluteus major muscle	90 µg/kg/3 hr × 1 day 90 µg/kg/6 hr × 2 days	14	5.140
5 th	November 1998	Drainage of cutaneous abscess of the left elbow	128 µg/kg/3 hr × 2 days 90 µg/kg/4 hr × 1 days 90 µg/kg/8 hr × 3 days	31	12.080
6 th	January 2001	Hemarthrosis right knee	90 µg/kg/4 hr × 1 days 90 µg/kg/6 hr × 2 days	14	5.140

rhage [3]. In our case, treatment with oral prednisone and cyclophosphamide was not effective. Immunoglobulins rapidly reduce the inhibitor titers [4], but in our patient were ineffective. rVIIa has proved to be effective in the control of hemorrhages these patients in 75% of the cases. rVIIa was used as the first line and only treatment for the hemorrhages and was effective in all the episodes. No adverse effects were observed. Nowadays rVIIa has been successfully used in acquired and congenital thrombopathies [5]. In no episode did we use complementary treatments. We used the manufacturer's recommendations as a guideline but paid special attention to the clinical situation and type of hemorrhage. In our case, it successfully replaced the traditional treatments consisting of other concentrates of coagulation factors and the use of antifibrinolytic drugs and platelet transfusions. Although there was a double alteration in the hemostasis of our patient, all of his episodes were satisfactorily controlled.

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Treatment of Two Patients With Acquired Factor VIII Inhibitors Using Cyclophosphamide and Prednisone

To the Editor: We describe two patients with acquired factor VIII inhibitors and bleeding who were treated successfully using a combination of cyclophosphamide and prednisone.

The first case is a 69-year-old man who was on prednisone 6 mg daily for rheumatoid arthritis and chronic renal impairment (creatinine ≈180 µmol/L) secondary to focal glomerulonephritis and amyloid. He presented with abdominal pain and extensive bruising over his trunk, abdomen, thighs, and buttocks. His hemoglobin was 50 g/L while he had a normal platelet count, normal PT of 12 sec (NR = 11–18 sec), and prolonged APTT of 88 sec (NR = 24–36 sec). Factor VIIIc was 8%, and a factor VIII inhibitor was detected at 128 Bethesda units (BU). He was treated initially with prednisone 60 mg daily together with red cell transfusion. Since after 4 weeks there had been no appreciable change in his APTT, factor VIII coagulant level, or inhibitor titre, oral cyclophosphamide 100 mg daily was added. Within 8 weeks his APTT had fallen to 48 sec, with an inhibitor titre of 3 BU. His prednisone dosage was tapered slowly to 15 mg over 5 months, however, the APTT increased to 75 sec, and the factor VIII titre to >32 BU. The cyclophosphamide was increased to 150 mg and prednisone to 25 mg daily. After a further 6 weeks, his APTT had fallen to 34 sec and the inhibitor titre to 2 BU, while 2 months later the factor VIII inhibitor was undetectable. Over the ensuing 12 months, the prednisone was tapered to 7.5 mg daily, and the cyclophosphamide to 0. The inhibitor has remained undetectable for more than 2 years subsequently.

The second case is a 40-year-old male with chronic hepatitis B and chronic renal impairment (creatinine = 300 µmol/L) secondary to diabetes and nephrotic syndrome. He presented with extensive bruising over his trunk and lower limbs. At the time his hemoglobin was 62 g/L with a normal platelet count, normal PT of 15 sec but a significantly prolonged APTT of 145 sec. Factor VIIIc was measured at 2% and a factor VIII inhibitor detected at a titre of 125 BU. He was treated initially with oral prednisone 100 mg daily together with intravenous immunoglobulin 1 g/kg and a continuous infusion of intermediate purity factor VIII concentrate. After 4 weeks his APTT remained significantly prolonged at 64 sec, with a factor VIIIc of 6%, and factor VIII inhibitor of 32 BU. He was then commenced on oral cyclophosphamide 150 mg daily in addition to the oral prednisone. After 8 weeks his APTT had fallen to 39 sec, with a factor VIIIc of 136% and an undetectable inhibitor. Over the next 6 months his

cyclophosphamide was reduced to 0 while his prednisone was tapered to 5 mg daily over 9 months. The APTT and factor VIIIc have remained normal 9 months later.

Acquired factor VIII inhibitors have been treated with a variety of measures including prednisone, cyclophosphamide [1], intravenous immunoglobulin [2], plasma exchange [3], porcine factor VIII [4], factor VIIa [5], and cyclosporin. In a study of 31 patients [1], factor VIII antibody disappeared in 5 out of 10 patients (50%) treated with cyclophosphamide after steroid failure. Neither of the two cases described above responded fully until the addition of cyclophosphamide. We confirm previous reports which indicate that for those patients with acquired factor VIII inhibitors who fail to respond to initial corticosteroid therapy, cyclophosphamide should be added.

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Origin of Hb S Antilles

To the Editor: Six variant hemoglobins (S-Antilles, C-Ziguinchor, C-Harlem, S-Providence, S-Oman, and S-Travis) have been described with both the sickle cell mutation (β^S glu \rightarrow val) and an additional amino-acid substitution in the same β -globin chain [1]. It is generally assumed that these double-substituted variants arose from crossing over between chromosomes carrying the Hb S mutation and the second substitution. However, no molecular genetic analysis has yet been carried out to validate such an assumption. Although such a mechanism is very likely for the most common variants, namely Hb Korlebu and Hb O-Arab, in generating Hb C-Harlem and Hb S-Oman and can be envisaged for the less frequent Hb Providence and Hb Dhofar in generating Hb S-Providence and Hb C-Ziguinchor, it is difficult to predict the origin of other double-substituted variants. Indeed, the second substitution in Hb S-Antilles, β^{23} val \rightarrow ile and in Hb S-Traville β^{142} ala \rightarrow val, had never been found alone. The alternative hypothesis is that the second mutation event occurred on one of the existing common β^S haplotypes, namely, the Benin, Bantu, Senegal, Arab-Indian, and Cameroon haplotypes [2].

In this study, we have explored the potential mechanisms that could have generated Hb S-Antilles by characterizing the β -globin gene cluster structure in 17 members of the original Caribbean family (Fig. 1a) in which this abnormal hemoglobin was identified [3]. Informed consent was obtained from all subjects who participated in this study.

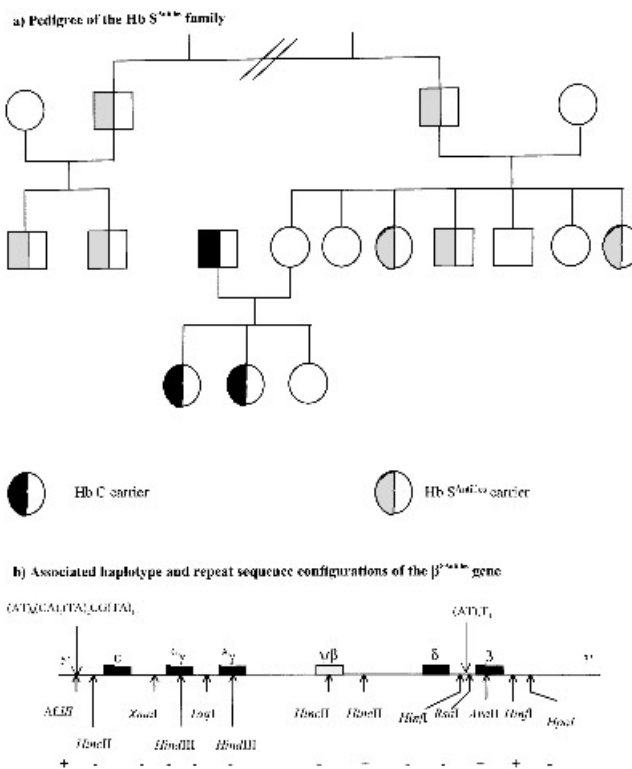


Fig. 1.

Hemoglobin status, as assessed by standard procedures, revealed that seven subjects were Hb S-Antilles carriers, three were Hb C carriers, and all others were normal. The presence of $\beta^{S-Antilles}$ mutations was confirmed by direct-nucleotide sequencing of the PCR-amplified β -globin gene segment.

The β -globin gene cluster haplotype analysis was performed as previously described [4] using 13 polymorphic restriction sites (Fig. 1b). The availability of pedigree data made the haplotype assignment unambiguous. The $\beta^{S-Antilles}$ gene was found to be associated with the classical RFLP-defined Benin β^S haplotype. Analysis of single-nucleotide polymorphisms within the structural β -globin gene by denaturing gradient gel electrophoresis showed that the $\beta^{S-Antilles}$ gene was linked to the same sequence framework (framework 2) as that of the Benin type β^S gene. As one patient heterozygous $\beta^A\beta^{S-Antilles}$, was homozygous for the RFLP-defined haplotype, we sequenced the simple sequence repeat polymorphism (at positions -10,623 and -10,570, GenBank HUMHBB numbering) in the hypersensitive site 2 of the locus control region and at position -540 5' of the β -globin gene. Both repeat configurations were identical to those linked to the β^S Benin haplotype [5].

In this study, we have shown that the doubly mutated β -globin gene variant $\beta^{S-Antilles}$ is linked to a haplotype sharing all the features of the so-called β^S Benin haplotype. Despite large-scale DNA screening of West Indies and Benin populations, we did not encounter the β^{23} val \rightarrow ile variant alone in any of the sample. Altogether our data strongly suggest that the transversion G \rightarrow A, leading to the amino acid substitution β^{23} val \rightarrow ile, occurred on a chromosome bearing a β^S gene of the Benin type haplotype, thus generating Hb S-Antilles.

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Successful Treatment With 2-Chlorodeoxyadenosine of Secondary Lesions of the Central Nervous System in Low-Grade Lymphoid Malignancies

To the Editor: Secondary lesions of the central nervous system (CNS) in low-grade lymphoid malignancies are very rare [1]. 2-Chlorodeoxyadenosine (2-CdA) is a purine analogue active in hairy cell leukemia (HCL) and in other low-grade lymphoid malignancies (chronic lymphocytic leukemia, Waldenström’s macroglobulinemia, low-grade non-Hodgkin’s lymphoma).

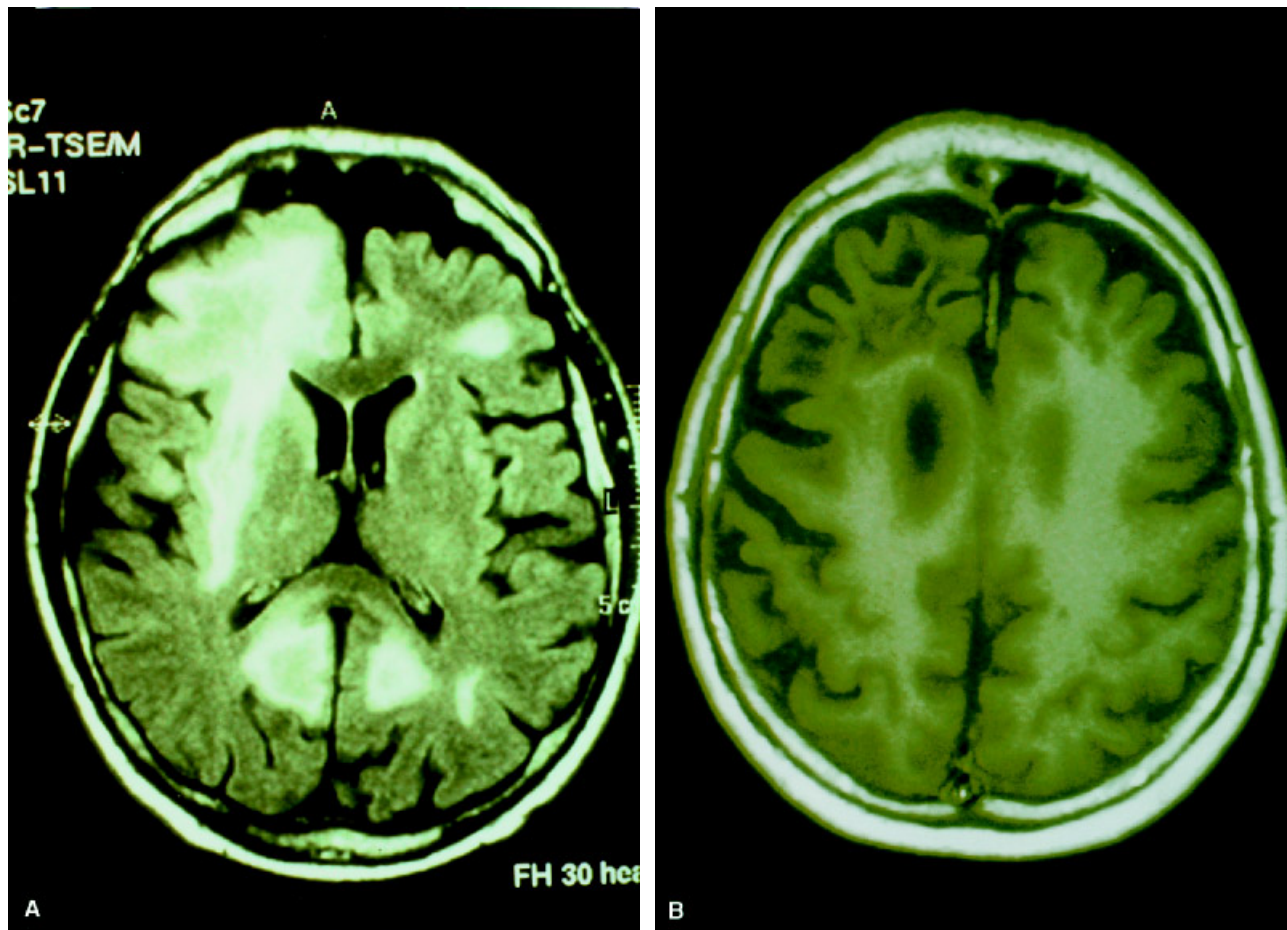


Fig. 1. Nuclear magnetic resonance (NMR) of the brain. (A) Multiple lesions of the white matter. (B) Complete regression after treatment. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com].

2-CdA penetrates into the cerebral spinal fluid (CSF) with a CSF/plasma concentration ratio of 25% [2]. These data form the rationale for use of 2-CdA in the treatment of CNS lesions in low-grade lymphoid malignancies. Two patients with secondary involvement of the CNS successfully treated with 2-CdA were reported. The first patient, a 56-year-old man with Waldenström's macroglobulinemia and biopsy-proven meningeal involvement, was treated with 4 cycles of 2-CdA, 0.1 mg/kg by continuous infusion for 7 days. NMR scans documented the complete resolution of the meningeal involvement [3]. The second patient, a 58-year-old woman with nodular centrocytic-centroblastic NHL and a secondary suprasellar mass involving the diencephalic and chiasmatic regions was treated with 2-CdA (0.14 mg/kg/day for 7 days/2 hr infusion and dexamethasone 0.3 mg/kg/day for 4 days) with complete regression of the mass [4]. We report on the third case, a 60-year-old man with HCL and multiple secondary lesions in the brain. This patient was first seen in 1975 at the age of 36 because of severe pancytopenia and a splenomegaly below the iliac crest. Bone marrow biopsy was consistent with the diagnosis of HCL, and splenectomy was carried out. Histological examination confirmed the diagnosis. The patient remained in good clinical conditions for the next 17 years. In 1992, at a periodic follow-up, a progressive increase of AST and ALT was documented. HCV antibody test was positive, hairy cells were identified in the peripheral blood smears, and bone marrow biopsy evidenced extensive infiltration. Liver biopsy was consistent with the diagnosis of HCV-related chronic hepatitis. The patient was treated with α -interferon (3 MU three times/week) for 6 months. In September 1998 he experienced progressive confusion and disorientation. The bone marrow biopsy evidenced extensive infiltration by hairy cells, and NMR of the brain multiple lesions of the frontal lobes; biopsy was not carried out because of severe thrombocytopenia and ipoprothrombinemia. The CSF was negative for cells, oligoclonal bands, mycobacteria, fungi, and aerobic and anaerobic bacteria; tests for antibody anti borrelia, cytomegalovirus, and viral genomic sequentia (JC virus) were negative. The first cycle of 2-CdA (0.14 mg/kg/day \times 7 days by a 3-hr i.v. infusion) was started on November 21st, 1998. The NMR, carried out on December 21st, evidenced a regression of the brain lesions (Fig. 1A). The second cycle was started on March 3rd, 1999. The two cycles were well tolerated without systemic or hematological toxicity. NMR of the brain, carried out in July 1999 and June 2001, confirmed the complete regression of the lesions (Fig. 1B). The bone marrow biopsy was hypocellular without evidence of HCL involvement. The patient, at the time of this writing, is symptomless.

No additional information related to the treatment of secondary lesions of the CNS in low-grade NHL treated with 2-chlorodeoxyadenosine is available in the literature at this time.

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Recombinant FVIIa in the Treatment of Bleeding in Acquired Hemophilia

To the Editor: Makris and colleagues recently reported a case of acquired hemophilia in a 62-year-old female unsuccessfully treated with recombinant FVIIa. This treatment had been administered because of major intra-abdominal bleeding after nephrectomy [1].

We treated an 81-year-old female in similar condition, who presented with a severe hematuria started 12 days before and which was complicated by a severe anemia requiring 3 units of packed red cell transfusions. Physical examination did not reveal any other bleeding site, but the patient reported an extensive hematoma on the forearm that occurred spontaneously 2 months previously. The CT scan suggested a right renal tumor, and before nephrectomy, routine preoperative blood coagulation tests were drawn, showing prolonged isolated APTT at 57 sec (normal range 33-40 sec). As no previous history of bleeding was found in the patient or in her family, acquired hemophilia was suspected. Factor VIII level was detected at 0.05 U/mL, associated with the presence of a FVIII inhibitor scoring 56 Bethesda units. We decided to treat the acute bleeding and eradicate the autoantibody by immunosuppression simultaneously. The patient received 90 μ g kg⁻¹ every 2 hr of rFVIIa over 24 hr as first-line therapy, which allowed hematuria to stop entirely, and rFVIIa was continued, using the same dose, every 4 hr over 12 hr in association with oral tranexamic acid at a dose of 40 mg kg⁻¹ per day. Antifibrinolytic drug was administered over 15 days until the FVIII level reached 0.5 U/mL. Treatment of hemorrhage with rFVIIa has been very well tolerated and clinically rapidly effective, without any side effect [2].

Immunosuppressive therapy, including daily prednisolone 1 mg kg⁻¹ with cyclophosphamide 100 mg, provided a rapid decline of anti-factor VIII antibody and its complete disappearance after 70 days of treatment.

The current status of the patient at 5 months' follow-up shows that the inhibitor is still negative and her FVIII level is normal (1.5 U/mL). The CT scan shows no possible aspect of tumor, and therefore we conclude that the patient initially presented with a renal hematoma. Biological, radiological, and ultrasound investigations excluded underlying disease. In contrast to the Makris report, our patient did not undergo surgery and consequently presented less serious bleeding; moreover, the inhibitor level was lower. In addition, the use of the antifibrinolytic drug may have enhanced the effect of rFVIIa [3], and the rapid decline of the inhibitor would have perhaps been influenced by early immunosuppressive therapy, starting with the antihemorrhagic treatment.

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CD5-Negative Chronic Lymphocytic Leukemia or Monoclonal B-Lymphocytosis of Undetermined Significance?

To the Editor: We have read with interest the article by Wang et al. [1]. In support of their findings, we describe two similar cases diagnosed recently.

CASE 1

FJ was a 71-year-old female with incidental WBC being 18,300/ μ L with 42% neutrophils, 52% lymphocytes, 6% monocytes; hemoglobin 12.9 g/dL and platelets 217,000/ μ L since August 2001. She was asymptomatic, and examination was unremarkable. Flow cytometry of the peripheral blood showed monoclonal lymphocytosis co-expressing CD20/ κ light chain, FMC7 positive; CD4, CD8, CD5, CD23, CD10, and CD103 were negative. Bone marrow examination showed numerous scattered small lymphocytes phenotypically similar to the peripheral blood. Bone marrow karyotype was normal and fluorescence in-situ hybridization (FISH) did not detect any t(11;14) or trisomy 12. Computerized tomography (CT) of the chest, abdomen, and pelvis revealed no abnormality. No chemotherapy was started. Repeat hemogram and CT was unchanged another six months later.

CASE 2

SJ was a 76-year-old male with incidental finding of WBC being 19,800/ μ L with 50% neutrophils, 44% lymphocytes, and 6% monocytes; hemoglobin 15.4 g/dL and platelets 271,000/ μ L since November 1998. He was diagnosed with chronic lymphocytic leukemia (CLL) and treated conservatively by his primary physician. He was referred to this institution in January 2002. Physical examination was unremarkable. Flow cytometry of the peripheral blood showed monoclonal lymphocytosis co-expressing CD20/ λ light chain, FMC7 positive; CD4, CD8, CD5, CD23, CD10, and CD103 were negative. Bone marrow examination was normal with a single benign lymphoid nodule. Bone marrow karyotype was normal, and FISH did not detect any t(11;14) or trisomy 12. CT of the chest, abdomen, and pelvis was normal.

Han et al. first introduced the term "benign monoclonal B-cell lymphocytosis" in 1984 [2], and Kimby et al. subsequently proposed the term "monoclonal B-cell lymphocytosis of undetermined significance" (MLUS) [3]. Regardless of the terminology, both groups described a benign subset of morphologically diagnosed CLL.

Since 1996 the diagnostic criteria of CLL have been revised to include positive B-cell surface markers with CD5 expression [4]. CD5 positivity has then become the hallmark of CLL. One may have classified our cases

as CD5-negative CLL as reported by Huang et al. [5]. However, to our opinion, further insistence of the term "CD5-negative CLL" is confusing. The immunophenotype of our cases is similar to that of marginal zone lymphoma, but there was no gastric or splenic involvement in our cases. The normal cytogenetic study and fluorescence in-situ hybridization also make mantle cell lymphoma less likely.

We agree with Wang et al. that a separate category of MLUS be used. We propose that MLUS to be defined by (i) monoclonal B-lymphocytosis with otherwise normal hemogram; (ii) no significant lymphadenopathy or hepatosplenomegaly; (iii) immunophenotype positive for B-lineage markers, CD19, CD20 and light chain restriction, and negative for CD5, CD10 and CD23; and (iv) normal bone marrow karyotype.

The relationship of MLUS to other B-cell lymphoproliferative disorders may be analogous to that of monoclonal gammopathy of undetermined significance and multiple myeloma. Careful clinical follow-up is recommended to monitor its tendency to progress to overt lymphoma/leukemia.

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