arabinoside (75 mg/m^2/day), and four daily doses of prednisolone (50 mg/m^2/day). This treatment was well tolerated and could be readministered after 2 weeks. After the second course, hemoglobin fell to 5.4 g/dl, and the patient suffered from severe angina pectoris. He then accepted the transfusion of packed red blood cells. Thereafter, he was treated with more aggressive regimens, with blood product support, but remission could not be achieved.

Our experience as well as that of Boggs [1] shows that effective or even curative therapy in Witnesses with acute lymphoblastic leukemia is possible without blood product support. On the other hand, we believe that effective chemotherapy for acute nonlymphocytic leukemia usually demands more aggressive regimens, which inevitably lead to severe cytopenia. The successful aggressive induction chemotherapy for acute nonlymphocytic leukemia without blood product support reported by Goldberg and colleagues [5] may be an exception and not applicable in general. Low-dose cytosine arabinoside may offer an alternative in the treatment of Witnesses with acute nonlymphocytic leukemia [4], although the remission frequency seems to be relatively low. Erythropoietin [6] and granulocyte colony-stimulating factor [7] seem to be attractive alternatives for supportive therapy, if they are accepted by these patients. At present, no general recommendations regarding the optimal management of Witnesses with acute leukemia can be given. Treatment should be individualized and should be based on the type of leukemia, local possibilities, and above all the wishes of the patient.

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Ciprofloxacin-Induced Neutropenia and Erythema Multiforme

To the Editor: We report the rare association of severe, reversible neutropenia and erythema multiforme with ciprofloxacin administration. A previously healthy 67-year-old woman presented to hospital with fever, chills, and abdominal pain of 1 day duration. She was scheduled for arthroscopy of an osteoarthritic left knee. The day prior to the procedure she developed fever, nausea, and a mild non-productive cough. The procedure was cancelled and she was given a course of oral ciprofloxacin 500 mg twice daily for a presumed respiratory tract infection.

Two days after starting ciprofloxacin, she developed an erythematous rash over her legs and trunk. Pathologic examination of a skin biopsy was consistent with erythema multiforme. She was hospitalized and given solumedrol by vein. On admission, ciprofloxacin was stopped as were her other medications: cimetidine, misoprostil, and Ansaid, all of which she had been taking for 3 months or more. The rash resolved within 24 hr and she was discharged.

A complete blood count prior to discharge showed hemoglobin 111 g/L, white cell count (WBC) 4.9×10^9/L, absolute neutrophil count (ANC) 1.5×10^9/L, and platelet count, 314×10^9/L.

Ten days after discharge she was readmitted with high fever, chills, and mild abdominal pain. Hemoglobin was 94 g/L, WBC 0.9×10^9/L and platelet count 378×10^9/L. She was transferred to our hospital for assessment after institution of empiric antibiotic therapy with cefazolin and tobramycin.

She had no history of blood dyscrasia, malignancy, or risk factors for HIV infection. Her only current illness was osteoarthritis of the right knee. On examination, temperature was 38.8°C and blood pressure 100/60 mm Hg. There was no rash. She had mild oral thrush. There was no palpable adenopathy. The remainder of her examination was normal. Hemoglobin was 85 g/L, WBC 1.0×10^9/L, differential showed lymphocytes 0.72, and monocytes 0.28 and ESR 48 mm/hr. The peripheral blood film showed rare neutrophils. Prothrombin and partial thromboplastin times were normal. A full biochemical profile and complement levels were normal; antinuclear antibodies and rheumatoid factor were negative. Coombs test was negative. Chest radiograph was normal. Urine and blood cultures were negative.

The patient was maintained on intravenous cefazolin and tobramycin. Bone marrow aspirate and biopsy obtained on the second hospital day showed severe marrow hypoplasia and markedly left shifted granulopoiesis with no malignant cells.

The patient became afebrile on day 7 and was discharged on day 10 with normal blood counts. Three weeks after discharge, blood counts were normal and there was no evidence of skin rash.

Adverse events related to ciprofloxacin are reported in 6 to 16 percent of patients and are predominantly central nervous and gastrointestinal [1–3]. Hematologic side-effects, including cytopenias, are reported in up to 1% of patients. Neutropenia is rare and occurs in less than 0.2% [3]. Despite this, only one previous case report of ciprofloxacin-induced neutropenia is documented in the English-language literature [4].

In our case, the temporal relationship between the start of therapy with ciprofloxacin and the onset of erythema multiforme and subsequently neutropenia strongly suggests a causal association. Although the patient was taking other medications that have also been associated with neutropenia, she had been receiving each of them for more than 3 months without complication.

Skin lesions are reported to occur in approximately 2% of patients receiving this antibiotic. Ciprofloxacin-induced erythema multiforme has been reported in one previous case in association with the development of acute interstitial nephritis [5].

In addition to its use in the treatment of gram-negative infections, recent publications advocate prophylaxis with ciprofloxacin in neutropenic patients [6]. In the latter setting, ciprofloxacin-induced neutropenia may be masked and result in possible prolongation of chemotherapy-related neutropenia.

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Lymphoma of Large Granular Lymphocytes

To the Editor: We read with interest the recent article by Sun and associates [1] reporting two patients with highly aggressive lymphoma of large granular lymphocytes. We would like to make a few comments and share our experience on this entity.

1. In our previous study on expression of natural killer (NK) cell markers in non-Hodgkin's lymphoma, 17 out of 51 cases of T-cell lymphoma studied were shown to express one or more NK cell markers [2]. Although Sun et al. counted these cases as lymphoma of large granular lymphocytes, we cannot make such a claim on all of these cases because cytologic preparations were not available in most of them. However, retrospective review shows cytoplasmic granules in the lymphoma cells in at least four cases [3]. According to our updated experience with CD56-positive lymphomas [4], we have indeed found cytoplasmic granules to be a characteristic feature in this cytologically heterogeneous group of tumors.

2. Immunophenotypically, the two cases described in their article appeared heterogeneous with one case being CD2+ CD3− CD56+ (probably true NK cells) and the other CD2+ CD3+ CD56+ (probably NK-like T-cells) [1]. The aggressive clinical course of these two patients further strengthens our suggestion that CD56-expression confers a poor prognosis in hematolymphoid malignancies [4], a finding also independently confirmed by another group of workers [5].

3. The second patient described in their article pursued a very unusual clinical course. This young male was initially diagnosed to have idiopathic thrombocytopenia, and splenectomy was followed by rapid progression of the underlying lymphoma [1]. We have previously reported a case with practically identical history; the immunophenotype is also similar CD2+ CD3+ CD16+ CD56+ CD57−, except that it is CD4+ instead of CD8+ [4,6]. Furthermore, our case is characterised by expression of S-100 protein. It will be interesting to know if S-100 protein can be detected in their case as well and whether its expression can identify a distinctive group of malignant lymphoma in which splenectomy heralds a rapidly progressive course.

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Author's Reply

To the Editor: The letter from Wong et al. raised several interesting questions:

1. Are all lymphomas expressing NK markers composed of large granular lymphocytes (LGL)? It all depends which NK marker is expressed. CD57+ cells separated by a fluorescence-activated cell sorter (FACS) were shown to be a homogeneous population of LGL [1]. Natural killer cells (CD3− CD56+) are LGL, but it has not been documented whether natural killer-like T-cells (CD3+ CD56+) assume consistently the morphology of LGL. CD3+ human thymocytes can be induced by interleukin-2 in vitro to express CD56 and acquire NK activity simultaneously [2]. Whether NK activity acquisition is accompanied by morphological change to LGL was, however, not mentioned in the above study. CD16 can be expressed in any cells carrying the Fc receptor of IgG, but it is confined mostly to natural killer cells with respect to lymphocytes. Unfortunately, many studies of lymphomas expressing NK markers did not examine tissue imprints to verify the existence of LGL. According to the experience of Wong et al. and that of ours, nevertheless, most, if not all, NK+ lymphoid cells assume the morphology of LGL. Since NK+ lymphomas are frequently highly aggressive, knowledge of the association between NK markers and LGL morphology is important, because a simple Wright-Giemsa stained tissue imprint showing LGL may give the hint of an aggressive lymphoma and further studies of NK marker should then be pursued.

2. Is CD56 an independent predictor for poor prognosis? The hypothesis that CD56 expression confers a poor prognosis is well documented by the work of Wong's group and is supported by the generally aggressive behavior of natural killer cell lymphoma. The question is whether CD56 is the indicator of an aggressive type of lymphoma which involves many prognostic factors or it is an independent indicator unrelated to other factors. The plan of Wong et al. of comparing CD56 positive with CD56 negative cases for a special group of lymphoma occurring in the upper aerodigestive tract [3] is a good idea, which may shed some light on the prognostic importance of CD56.

On the other hand, Chan et al. stated that "from the literature, no specific pattern of NK cell markers appears to be associated with aggressive disease" [4]. They felt that HLA-DR was more relevant to the aggressive clinical course. Kanovaros et al. further expanded the aggressiveness-related factors to include T-cell activation antigens CD25, HLA-DR, and the proliferation-associated antigen Ki-67 [5]. Imamural et al. also included two activation antigens, CD38 and HLA-DR, in the phenotype of aggressive natural killer cell leukemia/lymphoma [6]. It appears that a multivariate analysis of multiple factors is necessary to decide which factor, alone or in a group, plays an important role in the prediction of prognosis.

3. Does splenectomy trigger a rapidly progressive course? This is an interesting thought and deserves further studies to prove or disprove it. In addition, the prerequisite of some markers, such as S-100, to determine the influence of splenectomy is also an assumption which warrants further exploration. We did not test S-100 in our cases, but S-100 was found to carry a poor prognosis in cases of chronic lymphocytic leukemia of T-cell lineage [7].