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LETTERS AND CORRESPONDENCE

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Extrapulmonary Tuberculous Abscess in Chronic Lymphocytic Leukaemia (CLL) Treated With Fludarabine: Case Report and Review of Literature

To the Editor: A 58-year-old man presented 7 years ago with Binet stage II of CLL. Because of rapidly rising lymphocyte count of 46.9×10^9/L [normal range: $(1.5–4.0) \times 10^9$/L], he was treated with FND (fludarabine, mitoxantrone, dexamethasone), which resulted in recurrent neutropenia [1]. Six weeks after the fourth cycle of chemotherapy, he developed fever of unknown origin. Complete blood count showed hemoglobin 9.1 g/dL, platelets 58×10^9/L, leucocyte count 7.7×10^9/L [normal range: $(4–11) \times 10^9$/L]. Differential count showed neutrophils 2.3×10^9/L [normal range: $(2–7.5) \times 10^9$/L], lymphocytes 5.4×10^9/L [normal range: $(1.5–4) \times 10^9$/L], and absence of monocytes, eosinophils, and basophils. CD4 count was 0.2×10^9/L with a reversed CD4/CD8 ratio of 0.45:1. Serum IgG measured 346 mg/dL (normal >819 mg/dL), IgA 14 mg/dL (normal >70 mg/dL), and IgM 13 mg/dL (normal >55 mg/dL). Eight days after admission, he developed painful left thigh swelling. Computed tomography revealed hypodensities at the left rectis femoris, vastus intermedius, and vastus lateralis, which yielded pus on drainage (Fig. 1). Histological examination of tissue adjacent to the abscess revealed abundant Ziehl–Neelsen-positive mycobacteria, and subsequent culture confirmed *Mycobacterium tuberculosis*.

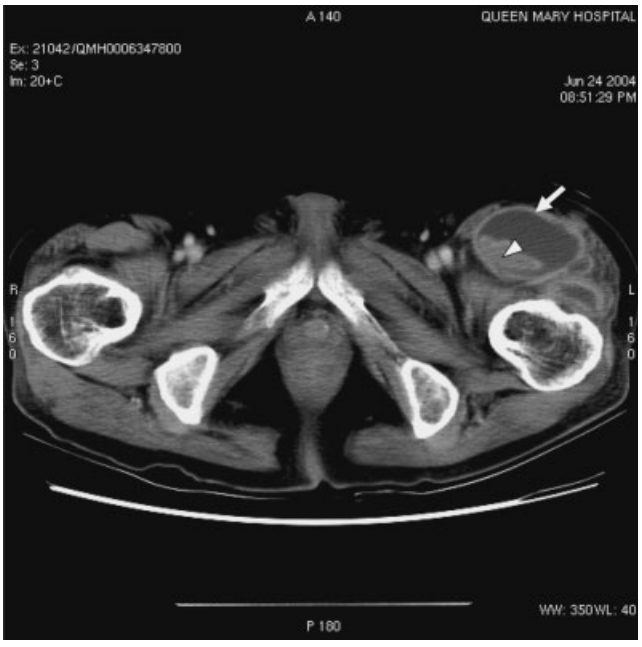

Fig. 1. Contrast CT scan at the level of femoral neck showed a well-defined fluid-containing lesion (arrow) is seen at the left groin region, just lateral to the femoral vessels and deep in the muscle layer. The left rectus femoris, vastus intermedius, and vastus lateralis are all involved. The presence of an intralesional debris rim (arrow head) and a rim of contrast enhancement suggests the lesion to be an abscess.

DISCUSSION

Our patient had refractory CLL complicated by extrapulmonary tuberculous abscess after fludarabine therapy. After initial infection with *M. tuberculosis* in an immunocompetent host, the bacillus is engulfed by macrophages with formation of granuloma [2]. This results in "containment" of the bacillus from dissemination. However, eradication of the intracellular mycobacteria requires γ-interferon from T lymphocytes, which induces production of antimycobacterial molecules by the activated infected macrophages [2]. Macrophages and T lymphocytes are thus central to the containment and eradication of mycobacteria. The CD4 lymphocytopenia and monocytopenia associated with recurrent leukocpenia might thus contribute to mycobacterial infection. However, as mycobacterial infection is an intracellular organism, hypogammaglobulinemia in this patient probably has a limited role in its pathohgenesis. Furthermore, it is noteworthy that at the time of tuberculous infection, our patient had a normal neutrophil count, thereby supporting the notion that mycobacterial infection is due to a defect in cellular immunity because of the depressed CD4 cell counts. However, in a disease such as CLL, which is associated with inherent immune deficiencies including T-cell dysfunction [3], it can be difficult to distinguish therapy-related and disease-related infections.

In the English literature are 13 case reports of mycobacterial infection complicating fludarabine therapy in patients with low-grade lymphoid malignancy, of which 5 involved extrapulmonary sites. Three out of these 5 reported cases were caused by *M. tuberculosis*, while atypical mycobacterium species were responsible for the other two cases (Table I). Almost half (3/7, 43%; in which outcome was reported) died of mycobacterial infection.

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TABLE I. Pulmonary Mycobacterial Infection in Patients With Chronic Lymphocytic Leukemia Treated With Fludarabine*

Year	Author	Organism	Site (P/E)	Outcome	Binet stage	Time to event[a] (months)
1988	Keating	*M. leprae*	E	No data	No data	No data
1991	Puccio	MTB	P	Fatal	No data	NA
1991	Puccio	MTB	P	Fatal	No data	NA
1992	Sanders	*M. bovis*	E (subcutaneous nodules)	Cured	III	5
1993	Keating	MTB	P	No data	No data	NA
1993	Hensel	Atypical mycobacterium	P	No data	No data	NA
1995	Fenchel	MTB	P	Cured	No data	NA
1995	Bryd	MAI	P	Cured	No data	NA
1995	Ghosh	MTB	P	No data	No data	NA
1998	Ruis	MTB	E (disseminated hemophagocytic syndrome)	Fatal	NA	4
1998	Costa	MTB	E (intracranial tuberculoma)	Cured	NA	11
2001	Morrison	Atypical mycobacterium	P	No data	No data	N/A
2001	Morrison	MTB	E (peritonitis)	No data	No data	No data

*Abbreviations: MTB, *Mycobacteria tuberculosis*; MAI, *Mycobacteria avium intracellulare*; P, pulmonary; E, extrapulmonary; NA, not applicable.
[a]Time to event, time (months) from start of fludarabine to mycobacterial infection.

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Fluid Retention During Arsenic Trioxide Treatment in Acute Promyelocytic Leukemia

To the Editor: Arsenic trioxide (ATO) is effective agent for acute promyelocytic leukemia (APL) with high remission induction rates of 88% for relapsed cases [1]. ATO produces differentiation of APL cells as well as *all-trans*-retinoic acid (ATRA) does. It is also known that ATO administration results in the development of fluid retention, which is followed by differentiation of APL cells and clinically similar to the retinoic acid syndrome induced by ATRA administration in 10–31% of patients [1,2]. However, some reporters indicated that they might be distinct phenomena because their clinical courses were different.

A 78-year-old man with APL in second relapse developed systemic edema and pleural effusion like retinoic acid syndrome during re-induction therapy with ATO. The protocol had been reviewed and approved by the institutional review board of Tokyo Medical and Dental University, and written informed consent had been obtained before starting the administration.

The clinical course is shown (Fig. 1). Neither cardiac nor renal insufficiency was detected. Dexamethasone was not effective. ATO administration caused differentiation of APL cells, and the patient finally achieved complete remission (CR). Fluid retention disappeared with discontinuation of ATO but appeared again along with re-administration of ATO for consolidation therapy after confirming CR. Its appearance was not related to the number of leukocytes in the peripheral blood. From the clinical features, we concluded that the fluid retention in this patient was different from APL differentiation syndrome and was an adverse effect of ATO itself.

Huang et al. reviewed 7 patients with relapsed APL treated with ATO and reported that fluid retention occurred in 6 patients (6/7, 86%) even during maintenance phase [3]. Thus, they suggested that the fluid retention might not be due to differentiation of leukemic cells and may differ from that observed in retinoic acid syndrome. However, the correlation between its incidence and the disease state was not mentioned clearly in the report. Recently, Unnikrishnan et al. reported that fluid retention developed in 13 patients (13/18, 72%) who were treated with ATO without renal and cardiac dysfunction [4]. These patients had not only APL but also other hematological malignancies whose leukemic cells did not differentiate with ATO treatment. According to the two reports mentioned above, it was concluded that ATO could induce fluid retention as a peculiar side effect, without any differentiation of leukemic cells. The present report clearly confirms this hypothesis.

Acute arsenic poisoning might cause capillary leak syndrome, which is accompanied by systemic edema [5]. Although the pathomechanism remains to be identified, ATO-induced fluid retention in APL is in agreement with this finding. In addition, the clinical finding of fluid retention caused by ATO in our case is different from retinoic acid syndrome by the following points: absence of fever and respiratory failure with hypoxemia and ineffectiveness of dexamethasone. Like steroids, ATO administration might induce hyperglycemia (18/40, 45%) [2]. Because long-term, ineffective administration of corticosteroids with ATO might result in severe complications, especially infection, it is important to distinguish between fluid retention from true retinoic acid syndrome.

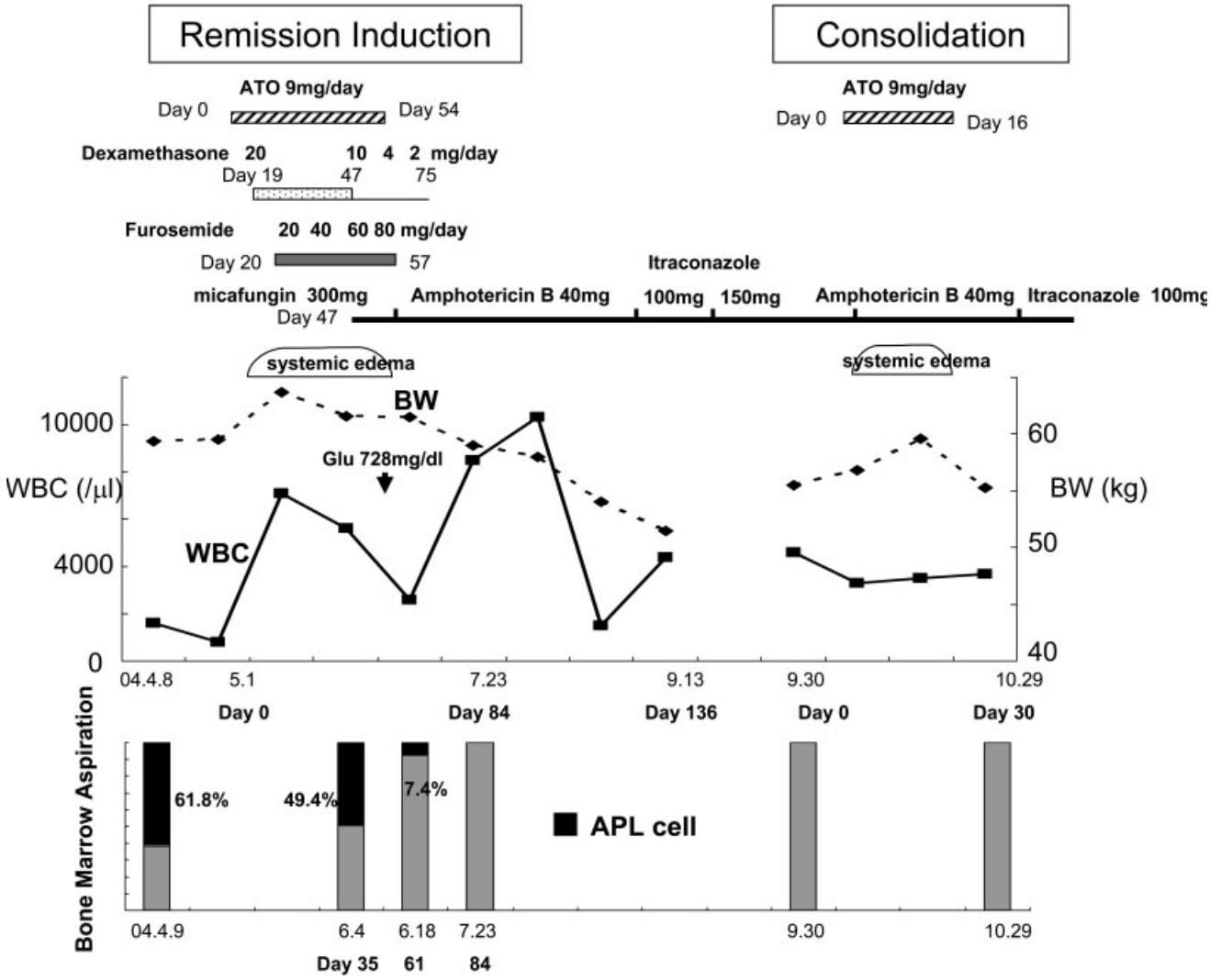

Fig. 1. Clinical course of a patient with APL developing fluid retention during ATO treatment. ATO, arsenic trioxide; BW, body weight; WBC, white blood count; Glu, glucose; APL, acute promyelocytic leukemia.

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Toxicity of Argatroban Overdose in a 65-Year-Old Man

To the Editor: We report a potentially important toxicity of argatroban that has not previously been described.

A 65-year-old male with ischemic and valvular heart disease underwent a successful mitral valve repair but developed heparin-induced thrombocytopenia in the post-operative period. The patient was consequently switched from unfractionated heparin to argatroban at an initial dose of 1 μg/kg/min, which was later adjusted to 0.3 μg/kg/min in the setting of a transient, unexplained deterioration in liver function [AST 689 U/L (normal range, 17–59 U/L), ALT

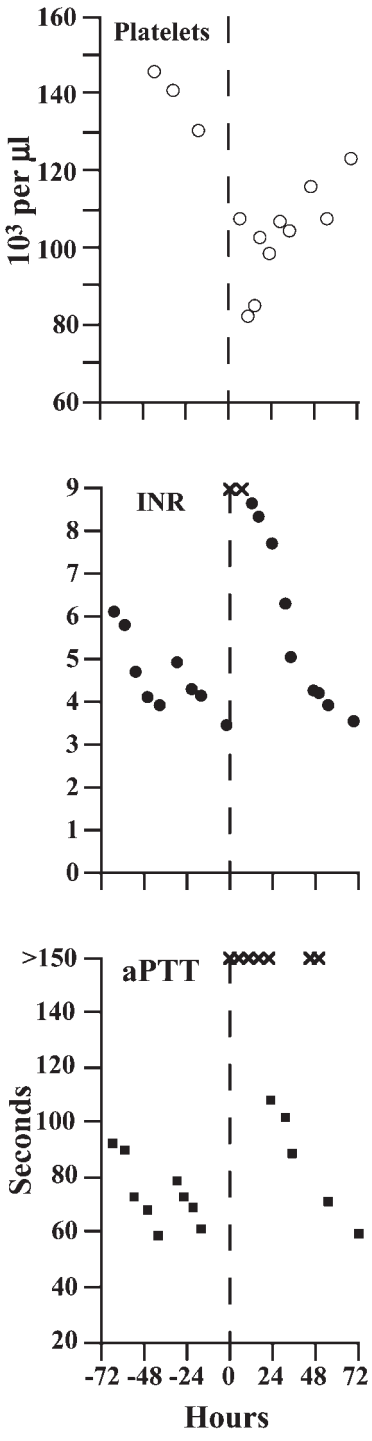

Fig. 1. Laboratory values for a 65-year-old man who received a large intravenous bolus of argatroban. The dashed line indicates the time of the bolus. aPTT and INR values exceeding the instrument range are indicated by "×".

334 U/L (normal range, 21–72 U/L)]. The patient remained critically ill in the post-operative period, requiring both ventilator and hemodynamic support.

On post-operative day 27, the patient inadvertently received a large intravenous bolus of argatroban over a 1-hr period (~225 mg; ~3.6 mg/kg). Upon discovery, the argatroban was immediately discontinued and the patient was closely monitored for hemorrhage and/or hemodynamic instability. There was no evidence of blood in tracheal aspirates, urine, or at the wound or arterial/venous access sites, although a small amount of blood was detected in the patient's stool. Interval laboratory tests indicated an immediate increase in aPTT and INR to levels exceeding the instrument range, followed by a gradual return to the therapeutic target range over the next 48 hr (Fig. 1). The patient's platelet count also fell from $131 \times 10^3/\mu L$ to $82 \times 10^3/\mu L$ but recovered in parallel with his resolving coagulopathy. No other potential cause for the thrombocytopenia was identified.

Argatroban is a direct thrombin inhibitor that, unlike heparin, does not require the presence of the cofactor antithrombin. Moreover, the anticoagulant effects of argatroban cannot be pharmacologically reversed. Argatroban is metabolized in the liver by hydroxylation and aromatization of its 3-methyltetrahydroquinoline ring with a terminal half life of approximately 39–51 min. The most common toxicities of argatroban relate to its coagulopathic effects, particularly in patients with aPTT values that exceed the therapeutic range. Although other toxicities have not been reported in humans, high doses of argatroban in laboratory animals (between 124 and 200 mg/kg) can result in a spectrum of neurological defects, including paralysis, convulsions, coma, and death.[1] A single in vivo study in human volunteers suggests a potentiating effect on plasma NO levels,[2] but other evidence indicating that high levels of argatroban may mediate potentially important vasomotor effects remains controversial.[3,4]

As our patient did not display any vasomotor or neuropathic dysfunction, we conclude that the chief risk of massive argatroban overdose in humans is related to its known anticoagulant effects. In addition, our observations suggest that patients receiving supratherapeutic doses of this agent may develop a transient thrombocytopenia that can further threaten the patient's hemostatic integrity, and indicate that platelet counts should be closely monitored in this setting.

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