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LETTERS AND CORRESPONDENCE

Philadephia Chromosome?

To the Editor: I am puzzled by the comment of Gürkan and Genç [1], in their description of a case of Bardet-Biedel syndrome, that a Philadelphia chromosome was detected. The Philadelphia chromosome is a derivative chromosome 22, resulting from a t(9;22)(q34;q11) translocation. This abnormality would not be expected in a patient with this syndrome and the fact that *BCR-ABL* fusion was not detected by PCR indicates that a Philadelphia chromosome was not present. Some further explanation appears to be needed.

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Reference

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Response to "Philadelphia Chromosome?"

To the Editor: We think that the presence of Philadelphia chromosome is rather unlikely an explanation for pancytopenia and lacks clinical significance in this case. The patient had completely recovered with appropriate treatment as mentioned before. The fusion gene produced by the BCR-ABL protein is leukemogenic, however, there are also reports demonstrating that BCR-fusion transcripts can be seen at very low frequency in the blood of healthy persons [1,2]. Absence of the fusion transcript might be due to small quantity of the clone, since Philadelphia chromosome was reported as positive only in few metaphases in our case. These observations suggest that the presence of the Philadelphia chromosome alone does not mean instant cancer or may not be sufficient to cause leukemia.

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Hyperammonemia and Encephalopathy in Patients With Multiple Myeloma

To the Editor: In recent years, a few case reports of hyperammonemic encephalopathy due to multiple myeloma (MM) have been published, but its prevalence and clinical significance remain unknown. We screened the database of the Myeloma Institute for Research and Therapy at the University of Arkansas for Medical Sciences, and we

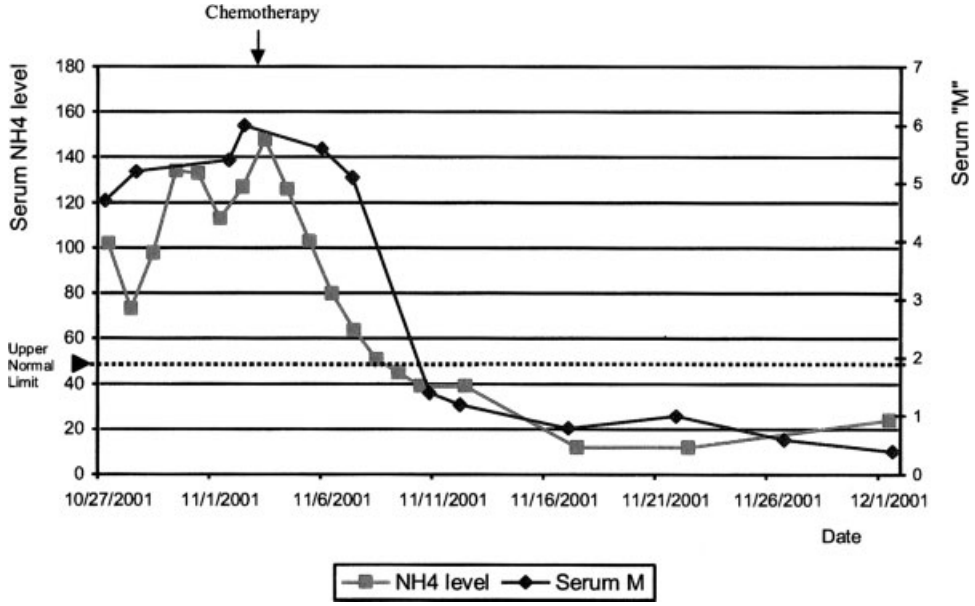

Fig. 1. Serum ammonia and serum paraprotein (M spike) levels in a patient with multiple myeloma treated with chemotherapy.

found 279 MM patients with altered mental status and available serum levels of ammonia (NH_4). Treating physicians requested the latter test as part of laboratory work-up used in the differential diagnosis of altered mental status.

Seventy patients were found to have hyperammonemia related to liver dysfunction. Among 209 MM patients with altered mental status and no evidence of liver dysfunction, the median serum NH_4 level was 21 μmol/l (range, 1–148). Only 8 patients (3.8%) were found to have encephalopathy associated with a serum NH_4 level >47 μmol/l (upper limit of institutional normal range). Although hyperammonemia could have contributed to the encephalopathy in all 8 patients, it was the single responsible factor only in two cases, because the remaining 6 patients had concomitant factors, such as hypercalcemia (1 patient), plasma hyperviscosity (1 patient), and CNS disease (4 patient), either alone or in combination, which could account for their altered mental status.

In one of those 2 patients with hyperammonemic encephalopathy and no other causes of altered mental status, tumor cytoreduction with chemotherapy was accompanied by a rapid normalization of both NH_4 levels (see Fig. 1) and mental status. No lactulose nor antibiotics were used.

Our report, which includes the largest number of patients with MM and an available serum NH_4 level, found that hyperammonemia is a rare finding in MM, because it was present in only 3.8% of 209 MM patients. This finding is consistent with the report of Matsuzaki et al. [1], who evaluated the NH_4 level in 85 MM patients, and found six cases (7%) of hyperammonemia. Nonetheless, hyperammonemic encephalopathy should be included in the differential diagnosis of altered mental status in MM patients, along with more common causes, such as sepsis, hypercalcemia, drug effect, and hyperviscosity syndrome.

The pathophysiology of hyperammonemia in MM is largely unknown. In vitro studies have demonstrated that myeloma cells in culture can produce excess NH_4, as a result of an altered amino acid metabolism [2,3]. Of note, 4 of our 8 patients with hyperammonemia and encephalopathy had also tumor involvement of the CNS, an event that has an overall incidence of $\sim 1\%$ in the course of MM [4]. We do not know the significance of this association.

Traditionally, the treatment of symptomatic hyperammonemia has involved restriction of dietary protein, antibiotic therapy (to inhibit the intestinal growth of urea-splitting bacteria), the use of nonabsorbable disaccharides, such as lactulose (to reduce the nitrogen load from the intestinal lumen), and, in severe cases, hemodialysis [5]. Here we have shown that in the presence of MM-related hyperammonemia, effective tumor cytoreduction results in a rapid normalization of both altered mental status and NH_4 levels.

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Chronic Myeloid Leukemia Following Radiotherapy for Carcinoma of the Cervix: Report of a Case and Brief Review of the Literature

To the Editor: The risk of second malignancies after radiotherapy (RT) is well described. Nevertheless, cases of secondary chronic myeloid leukemia (CML) after therapeutic RT have been rarely reported, although epidemiological studies have demonstrated a relationship between radiation exposure and CML after a latency period of 2–25 years in atomic bomb survivors as well as in patients receiving RT for different diseases [1].

Here, we describe the case of a patient with Philadelphia (Ph)-positive CML, 4 years after successful radiation treatment for uterine cervix carcinoma and briefly review the literature.

A 51-year-old woman presented with a hyperleukocytosis in December 2003. The hemogram was as follows: leukocytes 59.7×10^9/l (56% neutrophils, 19% stab, 11% metamyelocytes, 3% myelocytes, 1% promyelocytes, 1% blasts, 6% lymphocytes, and 3% erythroblasts), 680×10^9/l platelets, and 9.4 g/dl Hb. A bone marrow aspiration showed 1.3% myeloblasts, immature megakaryocytes, and increased cellularity with myeloid hyperplasia. The lactic dehydrogenase level was 1,086 U/l (normal: 200–900 U/l); other routine chemistry tests were unremarkable. Cytogenetic analysis demonstrated the presence of the Philadelphia chromosome t (9;22) (q34;q11) on 10 metaphases. Molecular analysis by polymerase chain reaction of the DNA from the bone marrow confirmed the classical bcr–abl rearrangement. She is currently in hematological and molecular remission with Gleevec 400 mg/day.

Past medical history included a hysterectomy plus RT for uterine cervix carcinoma in 2001 (Stage T2, TNM classification). A total dose of 5,000 cGy had been delivered on the pelvis (upper limit L5-S1). After this time, a right nephrostomy was required for treatment related urethral narrowing. No chemotherapy (CT) had ever been used in this patient.

Cancer treatment modalities, including RT and CT, could themselves increase the risk of developing secondary malignancies [2]. There is no defined definite radiation dose threshold for the induction of secondary malignancy after external beam RT in the literature. And there is little difference in the relative risk over the dose ranges from 2 to 80 Gy [2], although higher doses of radiation might increase the risk of bone and soft tissue sarcoma [3]. An increased risk of developing leukemia in women who have been treated with radiation for cervical cancer has been noted previously, but the dose–response relationship is complex. The risk increases with doses up to about 4 Gy and decreases at higher doses [4,5]. Any quantitative estimate of the cancer risk must involve some sort of model or assumption to allow an extrapolation to low doses, and any risk estimate is subject to debate and doubt [3].

This case of Philadelphia (Ph)-positive CML, 4 years following irradiation for uterine cervix carcinoma confirms that there is no defined definite radiation dose threshold for induction of secondary malignancies.

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Abdominal Pain and Syndrome of Inappropriate Antidiuretic Hormone Secretion as a Manifestation of Visceral Varicella Zoster Virus Infection in a Patient With Non-Hodgkin's Lymphoma

To the Editor: Lesions of varicella zoster virus (VZV) disease are usually limited to a few dermatomes. However, in immunocompromised patients, disseminated cutaneous and visceral involvement occurs. We report here a rare case of such a disseminated disease with manifestation of severe abdominal pain and syndrome of inappropriate anti-diuretic hormone (SIADH), which occurred 2 months after completion of conventional chemoradiotherapy for non-Hodgkin's lymphoma (NHL).

A 65-year-old woman was diagnosed as having diffuse large B-cell lymphoma of stomach origin. The clinical stage was II1 by the Lugano classification, and the International Prognostic Index score was low. HIV test was negative. She received chemotherapy consisting of three cycles of cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP), followed by radiation at a total of 40.5 Gray to the involved field, and a complete response was obtained. Two months later, she was re-admitted to our hospital because of severe abdominal pain lasting 2 days.

Her vital signs and physical examination were normal. Laboratory examination revealed prominent hyponatremia (Na 122 mmol/l, normal 138–146) and mild liver injury (GOT 74 U/L, normal 13–33; and GPT 63 U/L, normal 6–27). The serum osmolarity was 262 mOsm/kg, and urine osmolarity 532 mOsm/kg, which was consistent with SIADH. The pituitary size and intensity was normal but the occipital lobe of the cerebrum showed a high intensity on brain magnetic resonance imaging. In spite of fluid restriction, hyponatremia and her pain deteriorated. On the sixth hospital day, a subtle vesicular skin lesion on her abdominal wall was observed. We reasoned that her complaint might be attributed to the visceral involvement of VZV extending to the peritoneum, liver, brain, and skin. Upon starting treatment with acyclovir at 1,500 mg/day, her abdominal pain and hyponatremia improved, and she was discharged on the 14th hospital day. Polymerase chain reaction (PCR) for VZV of her peripheral blood and cerebrospinal fluid taken before acyclovir therapy was later found to be positive. The number of CD4-positive lymphocytes was 191/μL, and this low level has been maintained for as long as 1 year. The complete remission of NHL was also maintained throughout the episodes.

The occurrence of disseminated VZV including visceral involvement has been limited to immunocompromised patients; after stem cell transplantation (SCT), $\sim$17–50% of cases develop VZV infection [1,2], and, among them, visceral infection is rare (3.6% [2]). Especially, there are only a few VZV infection cases after SCT consisting of SIADH [3]. And only one case has been reported which developed along with severe abdominal pain and SIADH after conventional chemotherapy [4].

Storek et al. reported that the CD4-positive lymphocyte count after allogeneic SCT was inversely correlated with the infection score [5]. We suppose that her low CD4 count might have contributed to the visceral VZV infection. The reason why she showed such a low CD4 cell count is currently unknown.

It should be noted that this rare manifestation could occur even after conventional chemotherapy in NHL patients. Importance of recognition of this manifestation should be stressed because it is critical for the prompt diagnosis of the disease and its successful treatment.

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Methylprednisolone Pulse Therapy for Severe Immune Thrombocytopenia Associated With Infectious Mononucleosis

To the Editor: Although mild thrombocytopenia is commonly observed in cases of acute Epstein-Barr virus (EBV) infections, severe thrombocytopenia is extremely rare. Here, we describe an infectious mononucleosis (IM) case that developed life-threatening thrombocytopenia.

A 16-year-old woman was admitted to our hospital. Fever and cervical lymphadenopathy developed 10 days prior to admission. Although the symptoms resolved spontaneously, petechiae and purpura developed in the trunk 2 days before presenting to us. On examination, liver, spleen, or superficial lymphnodes were not palpated. Her tonsil and pharynx were normal. Numerous petechiae and purpura were observed in the trunk and extremeties.

Her white blood cell count was 10,200/mm^3 with 42.5% atypical lymphocytes. The hemoglobin concentration was 13.1 g/dl. Her platelet count was 1,000/mm^3. Serum AST was 224 IU/l and ALT was 309 IU/l. Urinanalysis showed proteinuria and microscopic hematuria. Antiplatelet antibody was positive and platelet-associated IgG was 577 ng/10^7 platelets (reference range, 9.0–25.0 ng/10^7 platelets). Anti-EB-VCA-IgG was negative and EB-VCA-IgM was positive. An abdominal ultrasonography disclosed moderate splenomegaly.

Severe epistaxis developed soon after the admission and it had to be treated by an otorhinolarygologist. Ten units of concentrated platelet rich plasma were transfused to control the bleeding. However, no increase of the platelet count was observed on the next day. Fifteen units of the platelet plasma were also transfused subsequent consecutive 3 days with minimum benefit. Methylprednisolone pulse therapy (1 g/day for consecutive 3 days intravenously) started on a day after the admission, followed by oral prednisolone. The platelet count increased gradually and it had exceeded above 50,000/mm^3 from 7 days after the

admission. Her symptoms resolved and oral prednisolone was tapered uneventfully without recurrence of thrombocytopenia.

IM caused by EBV usually resolves without problems but may occasionally be complicated by a wide variety of complication. Though mild thrombocytopenia occurs in ~25–50% of patients during the second and third week of illness, severe thrombocytopenia is exceedingly rare. Both hypersplenism and antiplatelet antibodies may contribute to thrombocytopenia [1]. The development of the antiplatelet antibodies may be related to polyclonal B cell activation induced by the EBV. In the present case, antiplatelet antibodies were detected and splenomegaly was found.

Although a number of cases with severe thrombocytopenia associated with IM have been published [1], life-threatening cases with platelet counts less than or equal to 3,000/mm^3 were limited [1,2–4]. Corticosteroids have been used for cases with severe thrombocytopenia after EBV infection although several weeks may pass before the platelet counts increases above 30,000/mm^3 [2]. Use of intravenous immunoglobulin (IVIG) refractory to corticosteroid was reported to be effective [3,5]. However, IVIG therapy is very expensive. In the present case, initial platelet count was 1,000/mm^3 and severe existaxis developed shortly after the admission. We started methylprednisolone pulse therapy because we considered this case to be life-threatening. Fortunately, the platelet count increased promptly and no fatal complication developed. Methylprednisolone pulse therapy might be considered as an initial therapy for immune thrombocytopenia with IM if the platelet count is extremely low.

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Complete Response to Alemtuzumab in a Patient With B Prolymphocytic Leukemia

To the Editor: A previously healthy 64-year-old male presented in April 2005 with worsening dyspnea on exertion, vague abdominal discomfort, and left shoulder pain of 2 months duration. He noted an enlarging abdominal mass. He denied fever, night sweats, nausea, or vomiting, but reported an unintentional 37 pound weight loss in the past year. Physical examination revealed massive splenomegaly, but no hepatomegaly or lymphadenopathy. A complete metabolic profile was normal. LDH was 816 units/l (normal 80–210). His white blood cell count was 68.2 $\times$ 10^9/l with 63% lymphocytes and 30% atypical lymphocytes. His hemoglobin and platelet count were 9.0 g/dl and 103 $\times$ 10^9/l respectively. The peripheral smear showed abundant prolymphocytes. A bone marrow aspirate and biopsy revealed a hypercellular marrow that was mostly replaced by a diffuse neoplastic proliferation of predominantly small lymphoid cells, many of which had prominent nucleoli. The malignant cells had bright surface kappa immunoglobulin light chain expression and co-expressed CD20, CD19, and CD23, and lacked the expression of CD10 and CD5 by flow cytometry. The neoplastic cells were negative for cyclin D1 by immunohistochemistry. The patient was diagnosed with B-cell prolymphocytic leukemia (B-PLL). Prior to starting chemotherapy with fludarabine and cyclophosphamide, he developed chest pain associated with dyspnea at rest. Evaluation revealed coronary artery disease with critical left main stenosis. He underwent an uneventful urgent four vessel coronary artery bypass grafting procedure. Cytotoxic chemotherapy was delayed to allow for wound healing. Due to worsening anemia, thrombocytopenia, and lymphocytosis, the patient was started on intravenous therapy with alemtuzumab. During the 12 weeks of therapy, the spleen size and peripheral blood counts normalized. At the end of therapy, a bone marrow aspirate and trephine biopsy confirmed complete remission. An autologous bone marrow transplant was recommended. After 10 months of appeals with the patient's insurer, he underwent an uneventful autologous peripheral hematopoietic stem cell transplant. He was in complete remission at the time of transplantation.

B-PLL represents 1% of lymphocytic leukemias [1]. Conventionally, alkylating agents, purine analogues or a combination of the two were used to treat this entity [2]. Recently there have been emerging reports of responses to the monoclonal antibody rituximab [3,4]. Little data is available about the role of alemtuzumab in the treatment of this disease, although significant activity in chronic lymphocytic leukemia and T-prolymphocytic leukemia has been reported. McCune et al. reported on 23 patients with relapsed/refractory chronic lymphocytic leukemia or prolymphocytic leukemia treated with alemtuzumab for up to 12 weeks. Among these patients five had prolymphocytic leukemia (B or T cell origin not specified). Among the four patients evaluable for response, 50 and 25% achieved a complete and partial response respectively [5].

We hereby report a treatment-naïve case of B-PLL that achieved a complete and prompt response with 12 weeks of alemtuzumab therapy. We believe that this agent deserves further evaluation in this disease.

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Rituximab as Preventive Therapy of a Clinical Relapse in TTP With ADAMTS13 Inhibitor

To the Editor: Acquired thrombotic thrombocytopenic purpura (TTP) is associated with circulating inhibitors to ADAMTS13 [1]. In these patients,

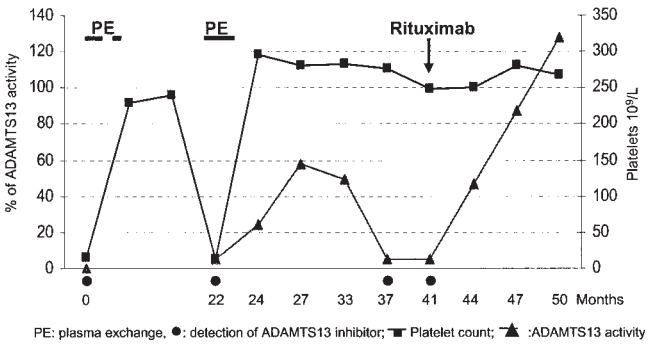

Fig. 1. Evolution of ADAMTS13 activity and platelet count during follow-up.

ADAMTS13 serum activity is usually above 5%. Plasma exchange (PE) is recognized as the standard therapy but is not effective in some refractory TTP and at least 30% of patients will experience one or several relapses. Predicting which patients will relapses remains a challenge as low levels of ADAMTS13 are not always associated to clinical relapse. Therefore adjuvant therapies have been proposed and most recently, rituximab has been shown to give promising results as an adjuvant curative treatment in acquired refractory or frequently relapsing ADAMTS13-deficient TTP associated with an inhibitor [2–4].

We report the case of a 27-year-old woman who presented in 2001 with TTP during pregnancy (hemoglobin 5 g/dL, platelets 16 $\times$ 10^9/L, undetectable haptoglobin levels, 2% of schizocytes on the blood smear, normal creatinine levels, and transient neurological symptoms). ADAMTS13 serum activity was undetectable, associated with an inhibitor. She recovered after a course of 10 PE and had a safe delivery (hemoglobin 12 g/dL, platelets 240 $\times$ 10^9/L). Her child was healthy without hematological abnormality. A relapse shortly after delivery was treated by a course of 7 PE. TTP relapsed in October 2003 (hemoglobin 5.2 g/dL, platelets 12 $\times$ 10^9/L, 1.4% of schizocytes on the blood smear without neurological symptoms) and was treated by a course of 31PE associated to a 1 mg vincristine infusion and a short course of corticosteroids. ADAMTS13 serum activity increased to 58% during the following at five months and anti-ADAMTS13 antibody disappeared. Follow-up showed a decrease of ADAMTS13 activity (5%) with recurrence of the inhibitor in January 2005. Despite the absence of any clinical or biological symptoms of relapse (hemoglobin 13.5 g/dL, platelets 248 $\times$ 10^9/L, normal haptoglobin, and LDH levels, absence of of schizocytes on the blood smear), we proposed to treat the patient by rituximab infusion, 375 mg/m^2 weekly for four weeks after informed consent, to prevent a new relapse. Treatment was well tolerated without any side effects. Low levels of activity were restored to normal and the inhibitor was negated (Fig. 1). At nine months the ADAMTS13 activity is at 128%. B cell count show the persistence of the B cell depletion (CD19 cells at 7/mm^3) with normal immunoglobulin blood levels.

Acquired TTP is a rare life-threatening disease whose prognosis has been improved by plasma exchange. However acute TTP and PE are associated with non negligible morbidity and mortality. Other treatments with immunosuppressive agents, splenectomy or high dose intravenous immunoglobulins have been proposed in regards of small series results. Recently, rituximab has been shown to be effective in refractory TTP. In a few patients this has been shown to prevent a relapse in the remission phase as single therapy [2,4].

Our case suggests the efficiency of rituximab as single therapy to prevent a relapse of TTP with ADAMTS13 inhibitor. The effect on long term remission, the time of administration, and careful selection of patients with high risk of relapses has to be ascertained by careful follow up and forthcoming studies as well as long term complications of rituximab.

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