Abstract  Transformation of chronic myeloid leukemia (CML) often results in acute myeloblastic or, less frequently, in precursor B-cell acute lymphoblastic leukemia (ALL). T-cell blast crisis is rare. Hypercalcemia has also been described as a rare complication of CML, but this usually occurs as a terminal event. Here we report a case of a 35-year-old woman who developed a CD4+/CD8+ T-cell ALL 2 years after the diagnosis of a typical Ph+ CML. Polymyositis and polyarthritis preceded by 4 months, and symptomatic hypercalcemia occurred just before blastic transformation, probably representing paraneoplastic manifestations of the disease.

Keywords  T-cell acute lymphoblastic leukemia · Chronic myeloid leukemia · Philadelphia chromosome positivity · Hypercalcemia · Polymyositis

Introduction  Chronic myeloid leukemia (CML) is a pluripotent stem cell disorder with the ability to differentiate into granulocytic, monocytic, erythroid, megakaryocytic, and lymphoid cell lines [32, 40]. Although it is recognized that in CML the malignant transformation usually occurs in a hematopoietic precursor common to the myeloid and B-cells, evidence is accumulating that CML may arise in a more primitive stem cell with potential to differentiate into the T-lymphoid lineage. Accordingly, it has been shown that T-lymphocytes from patients with CML might display fused bcr-abl sequences [19], and that CML may evolve into either a T-cell acute lymphoblastic leukemia (ALL) or a T-cell lymphoma [1, 2, 3, 4, 7, 9, 15, 17, 12, 13, 14, 18, 20, 24, 25, 26, 35, 38, 43]. Further, blasts from transformed CML may simultaneously show clonal rearrangements of the immunoglobulin heavy chain and T-cell receptor (TCR) chains genes [27, 42]. Late transformation of CML often leads to acute myeloblastic leukemia or, more rarely, to precursor-B ALL [8]. In contrast, T-cells are only exceptionally involved, and, to our knowledge, only a few cases of T-cell neoplasias have been reported as developing from CML [1, 2, 3, 4, 7, 9, 15, 17, 12, 13, 14, 18, 20, 24, 25, 26, 35, 38, 43]. Extremely rare cases of natural killer cell blast crisis have also been described [44].

In the present contribution we report a case of a young woman with Philadelphia chromosome positive (Ph+) CML who developed a CD4+/CD8+ T-cell ALL whose presenting features were polymyositis, polyarthritis, and symptomatic hypercalcemia.

Case report  A 35-year-old white woman was referred for leukocytosis in May 1992. On admission she had splenomegaly and a 2-month history of fatigue and bone pain. Peripheral blood (PB) counts were: hemoglobin level 10.0 g/dl, platelets 1042 x 10^9/l, white blood cell count 79 x 10^9/l (1.0% blasts, 2.5% promyelocytes, 12.0% myelocytes, 17.0% metamyelocytes, 34.5% neutrophils, 8.0% eosinophils, 10.0% basophils, 13.0% lymphocytes, 2.0% monocytes). Cyto genetic analysis of bone marrow (BM) cells showed a 46, XX, t(9;22)(q34; q11) karyotype. Other routine laboratory tests were unremarkable, except for an increased lactic dehydrogenase (1311 U/l; normal range of 230–460 U/l). Ph+ CML was diag-
nosed. Related BM donors were not available. The patient was treated with hydroxyurea (1 g daily per os, from May to June 1992) and α-interferon (3x10^6 U three times per week subcutaneously, from June to September 1992). Due to marked intolerance and poor compliance with α-interferon therapy she was then started on busulfan (2 mg daily per os).

By December 1993 she was hospitalized because of unproductive cough, severe myalgias, and polyarthralgias. At that time she was still receiving busulfan (2 mg daily per os), and the PB and BM remain consistent with CML in chronic phase. Chest radiography was normal and blood, urine, and sputum cultures were negative. The biochemical tests revealed increased aldolase 17.3 U/l (normal range: 1.2–7.6 U/l), creatinine-kinase 551 U/l (normal range: 24–195 U/l), glutamic oxaloacetic transaminase 87 U/l (normal range: 10–30 U/l), glutamic pyruvate transaminase 82 U/l (normal range: 10–36 U/l), γ-glutamyl transpeptidase 167 U/l (normal range: 7–32 U/l), alkaline phosphatase 409 U/l (normal range: 39–117 U/l), and lactic dehydrogenase 1093 U/l (normal range: 230–460 U/l). Other laboratory tests, including total calcium and inorganic phosphorus, were within the normal range, and there was no serological evidence of viral infection. Serum autoantibodies were negative, and immunoglobulin levels were normal. In view of the clinical features and increased serum levels of muscle enzymes the diagnosis of myositis was made.

In February 1994 the patient was readmitted because of fever, dehydratation, and disturbed consciousness. By that time a solitary soft tissue tumor (3x4 cm) appeared in the right upper femoral region. PB features were still consistent with CML in chronic phase. Analysis of spinal fluid was negative. Hypercalcemia was noted for the first time (4.44 mmol/l, normal levels 2.02–2.6 mmol/l) with normal levels of parathyroid hormone and 1, 25-dihydroxy-vitamin D₃ in the serum; skeletal radiography revealed no evidence of osteolytic lesions. Biochemical analysis continued to indicate active muscle destruction, and electromyography was consistent with a myopathic process. Treatment with disodium pamidronate (60 mg intravenously, every 2 weeks) and steroids (prednisolone, 100 mg daily per os) was then started for hypercalcemia. The tumor biopsy was unsuccessful and impossible to repeat, as it disappeared 1 week after starting corticotherapy. Duration of the episode was 1 week after starting corticotherapy. During the following month the patient suffered progressive weakness, weight loss, diarrhea, severe myalgias, muscle weakness and atrophy, polyarthritis, polyarthritis, and migratory polyarthritis.

By March 1994 the white blood cell count increased to 46.9x10^9/l, with 40% of atypical immature lymphoid cells, and the hemoglobin level and the platelet counts had rapidly decreased to 6.2 g/dl and 58x10^9/l, respectively. The BM was infiltrated by mononuclear cells with an immature T-cell phenotype: TdT+, CD1a+, CD7+, CD2+, CD5+, CD3+, TCRβ+, CD4+, CD8+, CD38+, CD71+, CD25+, CD34+. Analysis of spinal fluid was negative. In view of the clinical and laboratory picture typical ALL with normal levels of parathyroid hormone and 1, 25-dihydroxy-vitamin D₃ in the serum; skeletal radiography revealed no evidence of osteolytic lesions. Biochemical analysis continued to indicate active muscle destruction, and electromyography was consistent with a myopathic process. Treatment with disodium pamidronate (60 mg intravenously, every 2 weeks) and steroids (prednisolone, 100 mg daily per os) was then started for hypercalcemia. The tumor biopsy was unsuccessful and impossible to repeat, as it disappeared 1 week after starting corticotherapy. Duration of the episode was 1 week after starting corticotherapy. During the following month the patient suffered progressive weakness, weight loss, diarrhea, severe myalgias, muscle weakness and atrophy, polyarthritis, polyarthritis, and migratory polyarthritis.

In May 1994 she was readmitted to the hospital. She was then extremely ill and had a massive splenomegaly. Within a few days the white blood cell count reached 278.4x10^9/l with 97% blast cells. Southern blot analysis of PB cells showed the major breakpoint cluster region (bcr) gene rearrangement. The patient was started immediately on cytoreduction therapy with vincristine and showed partial response. The disease progressed shortly afterwards, and she died 1 month later with severe leukocytosis and sepsis.

**Discussion**

We report a case of a patient who developed a CD8+CD4+/CD1a+ (cortical TIII phenotype) T-cell ALL with an aggressive clinical course 2 years after the diagnosis of Ph+ CML. Polymyositis and polyarthritis preceded by 4 months and symptomatic hypercalcemia appeared just before the definitive diagnosis of blast transformation, probably representing paraneoplastic manifestations of the disease.

Review of the English medical literature since 1985 (Science Citation Index and Medline, 1985–2000) disclosed only 26 well-documented cases of CML evolving to or diagnosed simultaneously with T cell neoplasias, indicating that such association is quite rare [1, 2, 3, 4, 7, 9, 15, 17, 12, 13, 14, 18, 20, 24, 25, 26, 35, 38, 43]. Among these CML cases the majority were Ph+. Two cases of CML evolving to or diagnosed simultaneously with T cell neoplasias, indicating that such association is quite rare [1, 2, 3, 4, 7, 9, 15, 17, 12, 13, 14, 18, 20, 24, 25, 26, 35, 38, 43]. Among these CML cases the majority were Ph+. Two cases of T cell lymphomas on patients with Ph- CML were cited in which the myeloproliferative disorder proved to have bcr gene rearrangements by molecular studies [13, 24]. According to the literature, T-cell blastic crisis of CML may present as either extramedullary disease [1, 3, 9, 13, 14, 17, 18, 25, 26, 38, 43] or more rarely as leukemia [4, 12, 14, 24]. Extramedullary disease developed more frequently in lymph nodes [1, 3, 7, 9, 13, 14, 17, 18, 20, 21, 26, 35, 43] although extranodal masses have also been described [13, 38]. In the vast majority of cases the blast crisis occurred after a chronic phase following previous chemotherapy for the CML. In a few cases the two diseases were diagnosed simultaneously [17, 18, 26]. Three patients presented sequentially [17] or simultaneously [3] both acute myeloblastic leukemia and a nodal T-cell blast crisis. One patient developed sequentially B-cell ALL and a nodal T-cell lymphoblastic NHL [9].

Although it is virtually impossible to assess whether transformation into a T-cell neoplasm was related to previous chemotherapy, this appears very unlikely because of the short period between initiation of cytoductive treatment (May 1992) and blast transformation (March 1994). Moreover, chemotherapy-related leukemias are usually of myeloid origin. Furthermore, although additional chromosomal aberrations have frequently been found at the time of CML transformation [1, 9, 12, 13, 17, 24, 43], in the majority of cases, as in the case reported here, either the Ph chromosome or bcr-abl gene rearrangements or both have been demonstrated in lymphoid cells supporting a common clonal origin.

In addition to the rarity of CML evolving into T-cell neoplasias, this case has another remarkable feature in that polymyositis and polyarthritis preceding by 4 months the diagnosis of Ph+ T-ALL.

Although the possibility of arthritis and myositis being related to therapy for CML cannot be completely ruled out, this appears very unlikely as, to our knowledge, arthritis and myositis have not been previously reported in association with busulfan, and both hydroxyurea and α-interferon had been stopped more than 1 year before the episode. Thus polyarthritis and polymyositis probably represent paraneoplastic manifestations of the disease. Furthermore, although hypercalcemia did not precede the blast crisis – the tumor that appeared concurrently at the right femoral region, and that rapidly disappeared during corticotherapy was most probably a...