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Burkitt's Leukemia After Treatment of Primary Mediastinal Nonseminomatous Germ Cell Tumor

A 37-year-old man presented to us in February 2007 with reports of rising total leukocyte count (32×10^9/L to 92×10^9/L in 3 days). This had been detected in the course of a routine check after chemotherapy and surgery done for primary mediastinal germ cell tumor (GCT) 3 months earlier, in another hospital. His hemoglobin was 12 g/dL and platelet count was 25×10^9/L. There was no lymphadenopathy or hepatosplenomegaly. Previous to this the patient had been investigated in February 2006 for a 3-month history of breathlessness, cough, and expectoration. Chest x-ray and contrast-enhanced computed tomogram of the chest had revealed a large mediastinal mass with necrosis (Fig 1, arrows) and small pleural effusion (Fig 1). Computed tomography scan of abdomen and pelvis, and examination and ultrasound of testes were normal. Serum α-fetoprotein was 14,571 IU/mL and β-human chorionic gonadotropin was 157.6 mIU/mL. Tru-cut biopsy from mediastinal mass showed variegated areas characteristic of mixed GCT: undifferentiated cells in solid sheets with necrosis, and areas showing ectodermal (squamous epithelium), endodermal (mucosal glands), and mesodermal (cartilage and smooth muscle) differentiation as well as an immature component consisting of primitive neuroepithelium (Figs 2A to 2D). A diagnosis of nonseminomatous GCT (embryonal carcinoma and immature teratoma) was made. The patient was treated with etoposide 100 mg/m^2 days 1 through 5 and cisplatin 20 mg/m^2 days 1 through 5 every 3 weeks from April 2006. Bleomycin was omitted due to apprehension about pulmonary toxicity. Five cycles of etoposide and cisplatin had been given until July 2006; at this point serum markers had become normal. Contrast-enhanced computed tomogram chest revealed almost 70% to 80% reduction in the size of the tumor, with a residual mass measuring 9 cm that was invading pericardium and myocardium with effacement of coronary vessels. Fluorodeoxyglucose positron emission tomography showed mildly increased uptake along the margins of the mass. Given that the mass was considered inoperable, the patient was given two courses of chemotherapy with etoposide 100 mg/m^2 days 1 through 5, ifosfamide 2 g/m^2 days 1 through 5 with mesna, and cisplatin 20 mg/m^2 days 1 through 5. Surgical resection R0 type was then carried out in November 2006. Histopathologic examination showed residual immature teratoma. Postoperative computed tomography scan of the chest showed no residual disease and both markers continued to be normal. Our investigations in February 2007 showed 12% blasts in the peripheral-blood smear and 75% blasts in the bone marrow. The blasts had deeply basophilic cytoplasm with oil red-O–positive vacuoles (Fig 3, arrows); they were negative for myeloperoxidase and nonspecific esterase. Mitotic figures were present. The overall morphologic features were those of Burkitt leukemia. Flow cytometry showed blasts to be positive for CD19, CD22, CD 79a, HLA-DR, and CD45, and negative for all T-cell and myeloid markers. Fluorescent in situ hybridization technique was applied on interphase and metaphase cells using LSI MYC and LSI immunoglobulin heavy chain (IgH) dual-color, break-apart probes and CEP 8 probe (Vysis Abbott, Wiesbaden-Delkenheim, Germany). The IgH probe revealed normal copies of red/green signals. The signal pattern of *MYC* revealed two red/green signals (normal *MYC* copies; Fig 4, long arrows) and red signal at band 8q24 (Fig 4, short arrow) in 25% of interphase cells (large blast-like cells). Metaphase cells (15 of 15) with red/green signals and a red signal at 8q24 on copies of chromosome 8 indicated three copies of chromosome 8 with break in *C-MYC* followed by deletion of distal segment of *MYC*

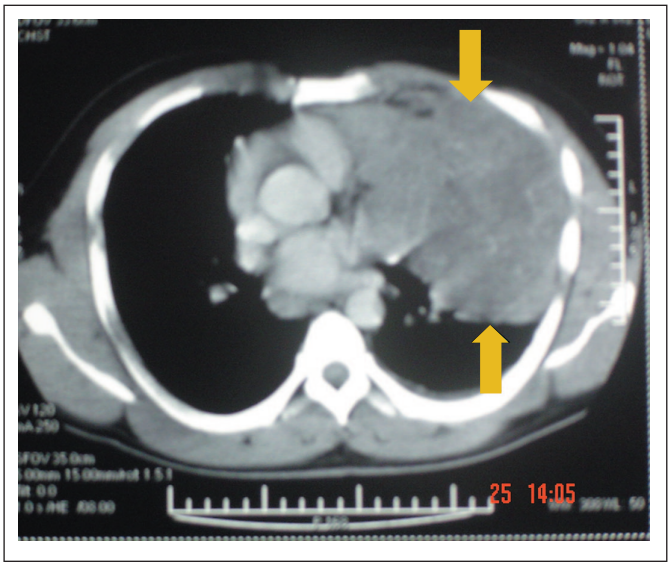

Fig 1.

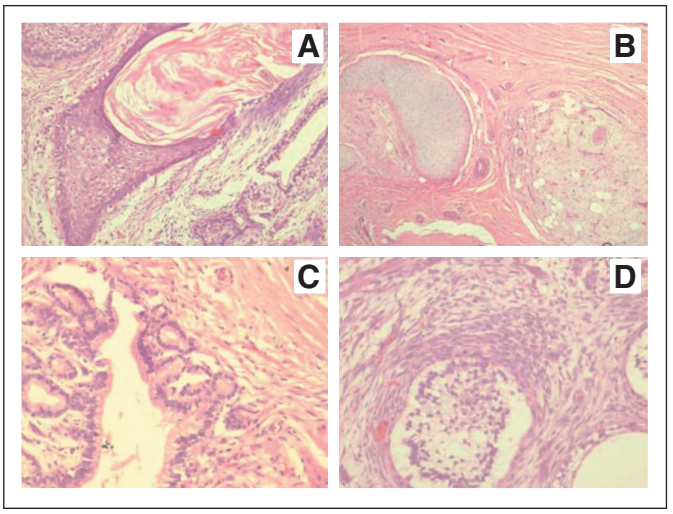

Fig 2.

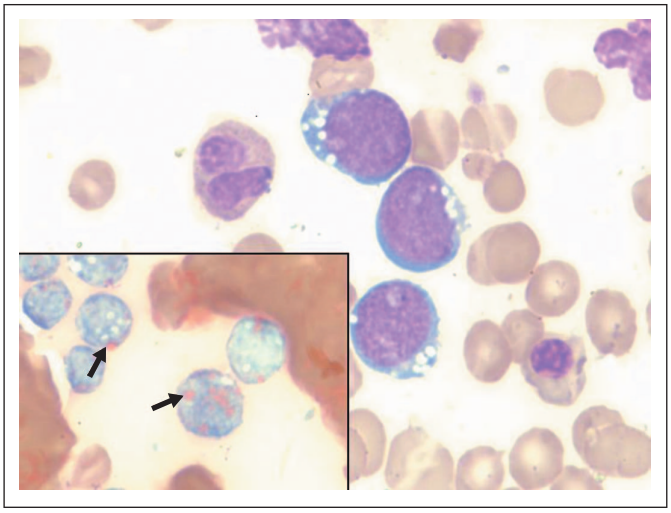

Fig 3.

(green signal) on a derivative 8 (Fig 4). The trisomy 8 was confirmed by fluorescent in situ hybridization with CEP 8. A final diagnosis of Burkitt's leukemia was made and the patient was started on cyclophosphamide, vincristine, doxorubicin, plus methotrexate; and ifosfamide, etoposide, and cytarabine.[1] Although he went into remission after cycle 1A, his tolerance to additional chemotherapy was poor; he developed grade 3 neurotoxicity, significant and prolonged liver and marrow toxicity, and disseminated intravascular coagulation. His drug schedule thus had to be modified significantly and curtailed, given that this protocol also contained etoposide and ifosfamide that he had received as part of his treatment for GCT. The patient had a frank relapse in August 2007 and died soon after.

Burkitt's leukemia has not been reported in a setting either of primary mediastinal germ cell tumor or postchemotherapy. The patient had received etoposide (total dose 3,500 mg/m^2), which has been implicated in the development, typically in 2 to 3 years, of secondary acute myeloid leukemia but not Burkitt's leukemia. Both the type of leukemia and the short period (3 months) postchemotherapy in which it developed set our patient apart from what is known in the literature.[2,3] There have been rare but well-established reports of acute megakaryocytic and acute myeloid leukemia, or rarely, non-Burkitt's acute lymphocytic leukemia (ALL), developing either simultaneously with, preceding, or following mediastinal nonseminomatous GCTs.[2,4-12] It is believed that some of these leukemias arise from hematopoietic foci in the GCT, a view supported by the demonstration of identical clonal aberrations; for example, the GCT-associated isochromosome 12p in both the GCT and the leukemia. Our patient had morphology typical of and flow-cytometric findings consistent with Burkitt's leukemia. Translocations involving *C-MYC* with partner gene, the *IgH* (14q32), the kappa light chain *IgK* (2p12), or the lambda light chain *IgL* (22q11) are common in Burkitt's-type ALL with L3 morphology. Our patient presented with *C-MYC* break followed by deletion of distal segment of *C-MYC* with no involvement of *IgH*, which indicates atypical *C-MYC* rearrangement. Unlike Burkitt's-like lymphoma (BLL), Burkitt's leukemia shows translocations such as t(14;18) in addition to t(8;14). Hidden *C-MYC* aberrations with no involvement of *IgH* have been described in rare cases of BLL.[13] Our case provides supportive evidence to the mechanism of *C-MYC* activation in BLL, which differs from that of Burkitt's lymphoma. The treatment of this patient was difficult. The patient had already received 700 mg/m^2 of cisplatin, 3,500 mg/m^2 of etoposide, and 12 g/m^2 of ifosfamide. His chemotherapy for Burkitt's leukemia had to be stopped after two cycles because he developed grade 3 peripheral neuropathy and prolonged recurrent disseminated intravascular coagulation.

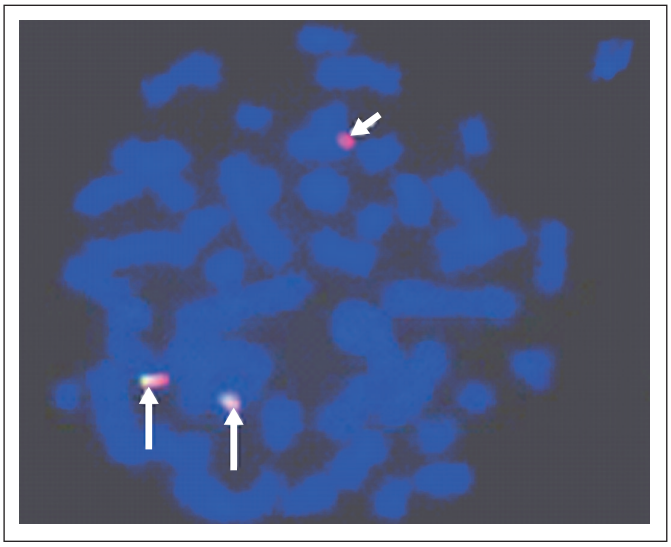

Fig 4.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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Invasive Pulmonary Aspergillosis Associated With Marijuana Use in a Man With Colorectal Cancer

In November 2006, a 65-year-old man presented for routine oncology follow-up with a 1-month history of cough, exertional dyspnea, and fever. Two years earlier, he had been diagnosed with colorectal cancer and treated with resection and adjuvant chemotherapy (fluorouracil and folinic acid). Nine months before his current visit, he was diagnosed with metastatic disease in his lungs and pelvis and had completed eight cycles of combination chemotherapy (capecitabine, irinotecan, and bevacizumab every 3 weeks), resulting in a significant reduction in tumor burden. At the clinic visit, his scheduled ninth cycle of chemotherapy was postponed, and he was prescribed a 7-day course of empiric moxifloxacin for presumed bacterial pneumonia. Despite this, he experienced progressive fatigue, increasing dyspnea, and small-volume hemoptysis, and presented to the emergency department. He had no other medical history of note. He was born in Canada and had no known exposure to tuberculosis. He took no regular medications. Although he had never smoked cigarettes, he had started smoking marijuana for the palliation of chemotherapy-induced nausea 6 weeks before presentation. Physical examination, including pulse oximetry and chest auscultation, was normal. The WBC (7.9×10^9/L) and neutrophil (5.2×10^9/L) counts were also normal, and no significant neutropenia had been documented during the course of the patient's chemotherapy. Cultures of blood and sputum for bacteria, mycobacteria, and fungi were negative. A computed tomography scan of the chest revealed a new 4.3-cm cavitary lesion (Fig 1, arrow) in the left lower lobe with surrounding ground-glass opacities. A computed tomography–guided fine-needle aspirate of the cavity was performed; microscopic examination demonstrated necrosis, inflammation, and masses of hyaline fungal hyphae with dichotomous branching and septations, compatible with *Aspergillus* species (Fig 2A). Fragments of plant matter, likely inhaled cannabis, were also present in the sample (Fig 2B). There were no malignant cells. Although no organisms were detected by conventional microbiologic techniques, polymerase chain reaction–based nucleic acid amplification and sequencing confirmed the presence of *Aspergillus fumigatus* in the aspirate. A 3-month course of voriconazole, the current standard therapy,[1] was administered for a diagnosis of invasive pulmonary aspergillosis. Six months after completing antifungal therapy, the patient has had total symptomatic and radiographic resolution of his infection.

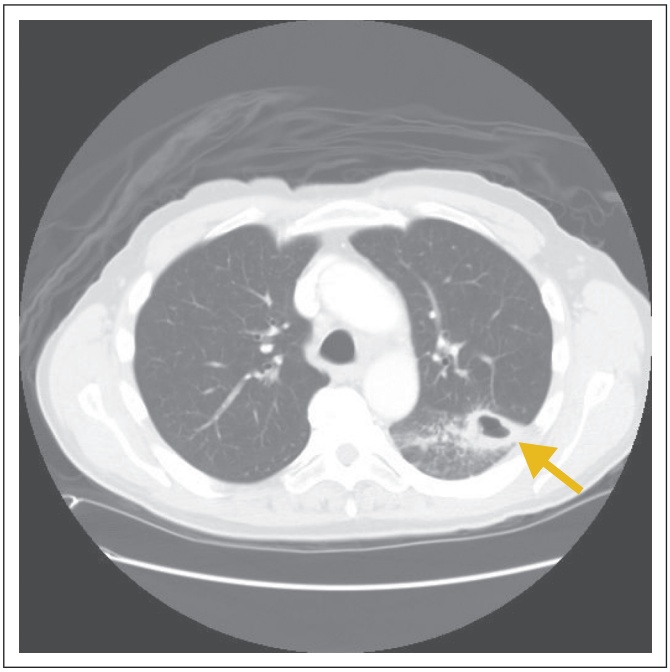

Fig 1.

Aspergillus is a ubiquitous filamentous fungus (mold) found worldwide in water, soil, and in particular, decaying vegetation. Invasive aspergillosis (IA) is a significant cause of morbidity and mortality in immunocompromised hosts. As in the patient we describe, infection is most often due to *A fumigatus*, and most frequently occurs in the lungs. Prolonged (> 3 weeks) and profound neutropenia is the most important predisposing condition for IA: patients with hematologic malignancies and hematopoietic stem-cell transplant recipients are at particularly high risk.[2] IA is less common among patients with solid tumors, but often occurs in the absence of neutropenia in this setting.[3] Other risk factors for IA include corticosteroid or anti–tumor necrosis factor therapy, solid organ transplantation, advanced HIV/AIDS, primary immunodeficiencies, chronic lung disease, and critical illness.[2] Inhalation of marijuana via smoking may also lead to invasive pulmonary aspergillosis, through both the contamination of the marijuana with fungal spores and the deleterious effects of marijuana

