

# Treatment-related MDS/AML in a patient after treatment for large-cell neuroendocrine lung cancer

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Secondary leukemia is a common late complication after exposure to cancer therapies such as chemotherapy and radiotherapy. With the increase in the overall survival of cancer patients over the past 3 decades, treatment-related malignant neoplasms have increased in incidence. Secondary leukemias due to breast cancer and Hodgkin lymphoma have been studied in detail, but to our knowledge only a few case studies have reported secondary leukemias with previous lung cancer.<sup>1-4</sup> Lung cancer is the leading cause of cancer death in the United States.<sup>5</sup> Since the overall survival (OS) as well as the progression-free survival (PFS) of lung cancer has improved, secondary malignancies, which are usually aggressive and have a poor prognosis, have become a common occurrence among survivors. The use of concurrent chemo-radiotherapy could increase the risk for secondary cancers. Here we report the case of a patient who developed treatment-related acute myelogenous leukemia (t-AML) with a likely prior myelodysplasia (t-MDS) after receiving combined chemo-radiotherapy for lung cancer.

## Case presentation and summary

A 62-year-old man presented to the hospital with complaints of fatigue and myalgia of several weeks duration. His previous medical history was positive for smoking, hypertension, hepatitis C, and successfully treated stage IIIA neuroendocrine lung cancer. Four years previously he had presented with complaints of right-sided chest pain for more than a year's duration and numbness of 3 days duration. Integrated PET-CT imaging revealed that he had a right lung mass. The biopsy was consistent with stage IIIA large-cell neuroendocrine lung cancer. He was managed with 2 cycles of neoadjuvant chemotherapy (cisplatin and etoposide), high-dose

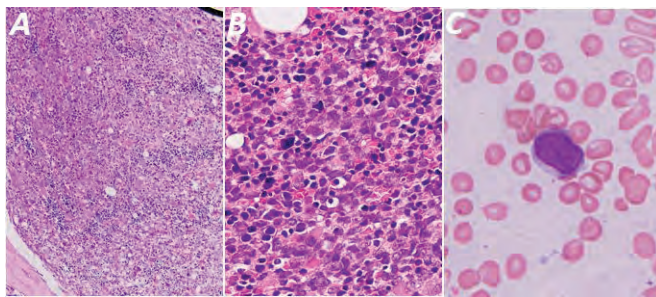
radiotherapy (RT; 66 Gy/33 Gy-fractions), and surgery (lobectomy) followed by another 2 cycles of chemotherapy with cisplatin and etoposide. After finishing his treatment regimen, the patient was kept on observation but was lost to follow-up after a few visits.

The physical examination and review of systems at his second presentation were grossly normal, with no lymphadenopathy or hepatosplenomegaly. Blood tests revealed hemoglobin of 8.4 g/dL (normal range, 12.5-16.3 g/dL), white blood cell count of 17,060/ $\mu$ L (normal, 3,600-11,200/ $\mu$ L), red blood cell count of 3.16 M/ $\mu$ L (normal, 4.06-5.63 M/ $\mu$ L), and a platelet count of <10,000/ $\mu$ L (normal, 159,000-386,000/ $\mu$ L). The results of the peripheral smear examination revealed 17% segmented neutrophils, 10% band neutrophils, 19% lymphocytes, 5% monocytes, 2% eosinophils, 7% basophils, and 3% metamyelocytes, with 37% blasts (Figure 1). Blood chemistry showed elevated creatinine (1.5 mg/dL; normal, 0.7-1.3 mg/dL), low albumin (2.5 g/dL; normal, 3.4-5.4 g/dL), low alanine aminotransferase (ALT; 8 U/L; normal, 10-40 U/L), and low serum uric acid (1.4 mg/dL; normal, 2.5-8 mg/dL).

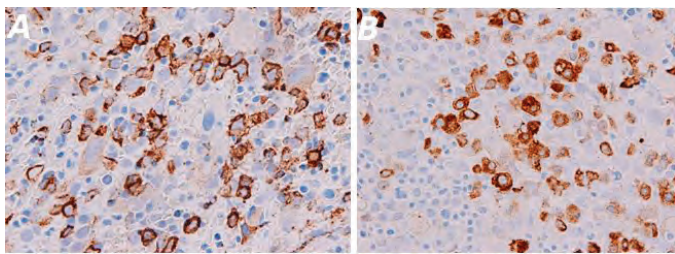
The bone marrow aspirate and biopsy showed hypercellular marrow (70% cellularity with 22% blasts in the cellular compartment) with decreased trilineage hematopoiesis (Figure 1). The special stains were positive for Periodic Acid-Schiff, reticulin, and iron; and the immunoperoxidase stains were positive for CD34 and myeloperoxidase (Figure 2).

Abnormal cells from cytogenetic study all had a deletion of bands 5q31-q33 in one chromosome 5, typical of MDS, and a derivative chromosome 17, formed apparently by replacement of 17p with an unidentifiable segment of another chromosome. The

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**FIGURE 1** H&E sections of the patient's bone marrow biopsy and aspirate smear. A and B, Microscopic appearances of the bone marrow biopsy and aspirate smear, respectively, showing a dense leukemic infiltrate (original magnification x100 and x400, respectively). C, Nucleated myeloblast with scant cytoplasmic granules (original magnification x1000).



**FIGURE 2** Immunohistochemical characterization of blasts in A, the bone marrow core biopsy for CD34 and B, myeloperoxidase (original magnification x400). The CD34 immunostain highlights the large blastic forms and the myeloperoxidase is immunoreactive in blasts and neutrophils.

loss of chromosome 17 p is usually associated with a p53 mutation or loss of normal p53 activity. Also seen were monosomy 3 or a derivative 3 minus most of the q-arm; hypodiploid cells (41 to 42 chromosomes) with rearrangements giving equivalents of a 7q deletion and a duplication/deletion in 11q; and a consistent monosomy of chromosomes 18 and 20. Fluorescence in situ hybridization (FISH) of interphase nuclei showed the 5q deletion (*EGRI* at 5q31) in 93% of cells, the deletion of 7q31 (D75486) in 11%, and the loss of a chromosome 20 (D20S108) in 17%.

The patient was diagnosed with t-MDS/AML with unfavorable cytogenetics. He was not a candidate for aggressive chemotherapy because of his poor performance status. The patient's white blood cell and blasts counts continued to increase. He was given hydroxyurea, which was discontinued after 5 days because of his low platelet count. His functional and neurological status continued to decline, and it was decided that hospice care would be the best option. He was transferred to a skilled nursing facility with hospice and passed away in the first week after discharge from the hospital.

## Discussion

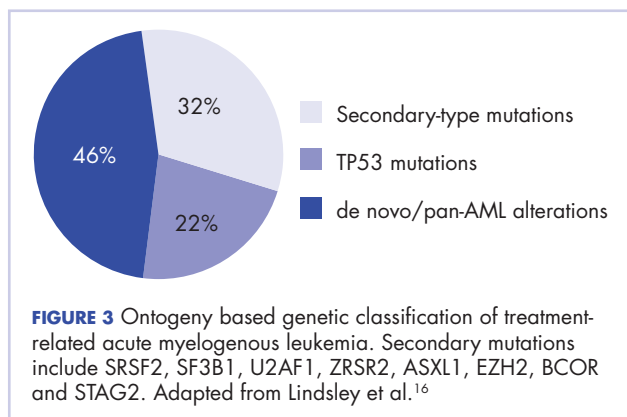
Treatment-related secondary malignancies are a major concern, especially for long-term cancer survivors. The risk of t-MDS/AML is related to the patient's age, the specific agents that were used to treat the patient, the dose administered, and the duration of the therapy. The cumulative incidence of t-MDS/AML after intensively treated lung cancer has been reported in the range of 14%-25%.<sup>3,4</sup> Therapy-related myeloid neoplasms were included in the World Health Organization's AML classification system in 2008 as a unique clinical syndrome encompassing t-MDS/AML and the myeloproliferative variant t-MDS/MPN. Two subsets were recognized. The first subset follows treatment with alkylating agents and/or RT and is associated with unbalanced loss of chromosomal material, particularly that of 5q and 7q. The second subset often follows treatment with topoisomerase II inhibitors and is characterized by balanced chromosomal rearrangements, particularly t(15;17), inv(16), t(8;21) and rearrangements in 11q23 and 21q22.<sup>6</sup> Latency periods between treatment and the onset of treatment-related malignancies vary: 5-7 years for the subset of unbalanced chromosomal aberrations, and 2-3 years for the subset of balanced aberrations.<sup>7</sup> When there is progression from t-MDS to t-AML, the succession occurs within a median interval of four months.<sup>8</sup>

Even with timely diagnosis and treatment, the prognosis of t-MDS/AML is poor, with a 5-year survival of less than 10%; and patients in the first subset (imbalanced aberrations) have a particularly poor outcome.<sup>6</sup> Patients in the second subset (balanced aberrations) may have an improved survival time depending on their karyotype. What underlies latency and survival times has been extensively investigated.<sup>9</sup> Cytogenetics is a strong indicator and can serve independently to predict survival.<sup>10</sup> The unfavorable karyotypes (median overall survival, 6 months) are: 5q-/-5, 7q-/-7; 3q21q26 abnormalities, abnormalities of 11q23, 12p, and 17p; and complex aberrant karyotypes involving 3 or more abnormalities.<sup>10</sup> A second independent predictor is thrombocytopenia on diagnosis, thought to reflect irreversible injury to hematopoietic stem cells by previous therapy.<sup>9</sup>

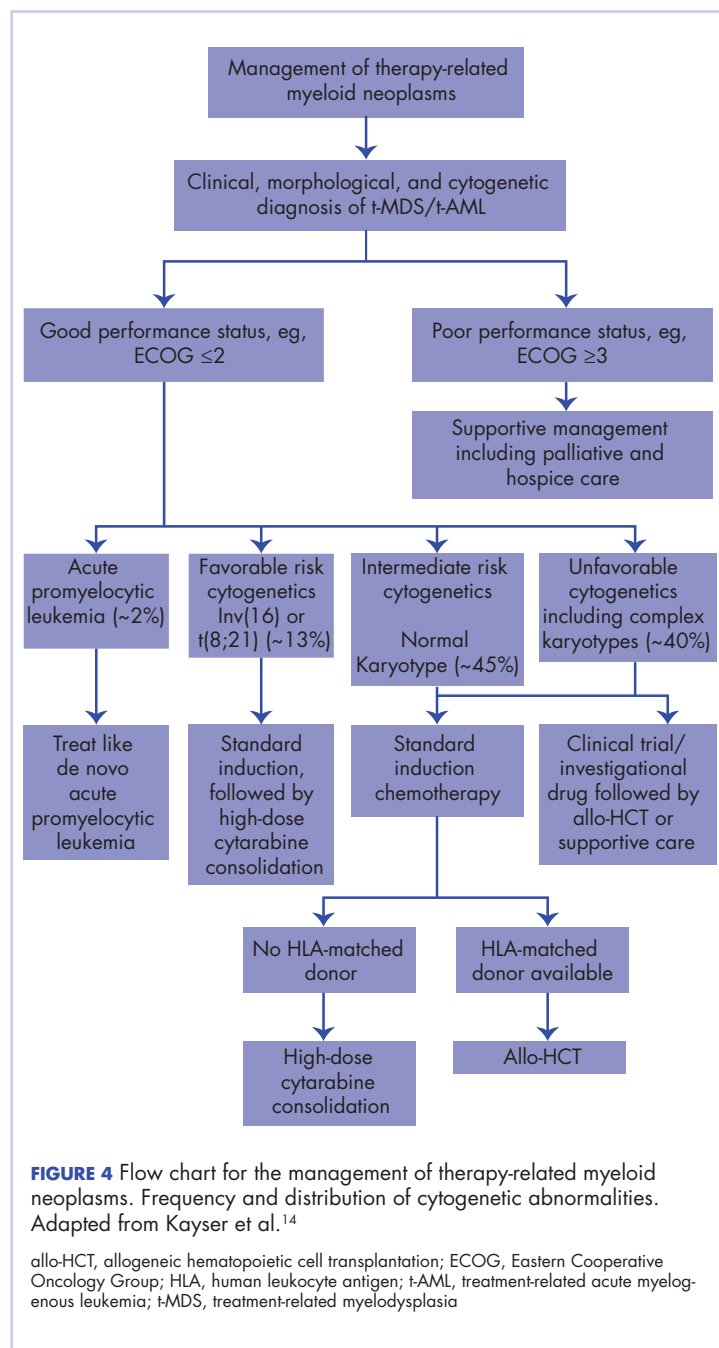
The treatment options for t-MDS/AML are limited because many patients are poor candidates for aggressive management. The primary treatment for patients with good performance status is induction chemotherapy followed by allogeneic bone marrow transplantation. This treatment should be considered as soon as possible, especially in younger patients.<sup>11-13</sup> Patients with favorable karyotype can be treated in a similar fashion like de novo AML involving induction and consolidation. Patients with unfavorable karyotypes account for the largest patient group with t-MDS/AML.<sup>14</sup> Those patients do not respond well to conventional therapy and should be put on a clinical trial with an investigational drug if possible.

To our knowledge, this is the first case report of t-MDS/AML following treatment for a large cell neuroendocrine lung cancer. The patient was at risk for t-MDS/AML from a combination therapy including alkylating agents, topoisomerase II inhibitors, and radiotherapy. His age (62 years) and the latency period of 4 years for the onset of t-MDS/AML were typical of treatment effects of alkylating agents/radiotherapy, and this was confirmed by cytogenetics and FISH. Despite exposure to etoposide, there were no balanced rearrangements of *MLL*; instead this gene was present in multiple copies. Following the distinction between t-MDS/AML caused by alkylating agents compared with topoisomerase II inhibitors, Pedersen-Bjergaard and colleagues have defined alternative genetic pathways to t-MDS/AML, refining their path analysis by noting the sequence in which chromosomal and genetic mutations occur.<sup>15</sup> Our patient belongs to pathway II (of 8), characterized by early appearance of *TP53* mutations and 5q-, then 7q- and *MLL* amplification. *TP53* mutation with complex karyotype is associated with therapy resistance and poor survival.<sup>16</sup>

The poor survival of patients such as ours raises the question of whether exposure to treatments causing secondary malignancies can be minimized or avoided. Two risks are involved: the risk that a treatment will cause t-MDS/AML and the risk of ineffective treatment of the primary malignancy. Over time, improvements in therapy have lowered the first risk, though the depletion of normal hematopoietic stem cells remains a determining factor.<sup>7</sup> As is evident, any substantial progress will come only through knowledge of the genetics underlying the initiation and progression of all forms of MDS and AML, including t-MDS/AML (Figure 3).<sup>16</sup> The genetics of myeloid malignancy, however, are extremely complex, including factors of individual variation, which itself includes questions of preexisting predisposition to t-MDS/AML. Remission states still carry chemoresistant, disease-driving mutations. At present, it is not clear whether known genetic findings can so explain the disease biology as to affect therapy and prognostic accu-



racy.<sup>16</sup> Figure 4 gives recommendations for the work-up and treatment of t-MDS/AML.



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