The Transdifferentiation of Mediastinal Germ Cell Tumor into a Myeloid Neoplasm in the Bone Marrow-Report of a Case and Short Review of a Diagnostic Pitfall

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Abstract

We present the case of a young male with a mediastinal non-seminomatous germ cell tumor who developed a severe thrombocytopenia, one year after initial diagnosis and surgical treatment and chemotherapy. Bone marrow morphology suggested myelodysplastic syndrome (refractory cytopenia with multilineage dysplasia). Cytogenetics of bone marrow showed near tetraploid karyotype, raising concerns about the diagnosis of MDS. The patient died within one month due to refractory disease and autopsy revealed a highly invasive germ cell tumor in the mediastinum and chest wall which showed the same cytogenetic abnormality seen in the bone marrow. The bone marrow collected at autopsy showed features compatible with acute myeloid leukemia. The implications of this transdifferentiation of a mediastinal germ cell tumor into an apparent hematological malignancy for correct diagnosis and appropriate treatment are discussed.

Keywords: mediastinal non-seminomatous germ cell tumor, hematologic malignancy, transdifferentiation

1. Introduction

Germ cell tumors (GCT) constitute only 1-2% of human cancers but are the commonest malignant tumors encountered in adolescent and young adult males (Ikdahl, Josefsen, Jakobsen, Delabie, & Fossa, 2008). Secondary hematological malignancies may occur in patients with testicular GCT as a result of prior chemotherapy (Nichols et al., 1985), but most hematological neoplasms arising in mediastinal GCT arise either shortly after the diagnosis of GCT or concurrently with the GCT (Hartmann et al., 2000; Nichols et al., 1985). In some of these cases there is no prior history of chemotherapy and the median interval between the two diagnoses is only about six months (Hartmann et al., 2000). These features do not support the notion of a chemotherapy induced secondary malignancy. Metastasis of mediastinal GCT to the bone marrow are rare (Chandra, Sagar, Raman, & Rajalekshmy, 2002; Orduz et al., 2005), but occasionally disease recurrence restricted to the bone marrow has been reported (Garbay, Durrieu, Bui, & Italiano, 2012). Here we present a case of mediastinal non-seminomatous-GCT, where the GCT itself appears to transdifferentiate into a myeloid malignancy resembling treatment induced myelodysplastic syndrome. Cytogenetic studies performed on the myeloid neoplasm and GCT show clonal identity between these morphologically diverse processes. The current understanding about the clonal relationship between the GCT and hematological malignancy is examined and the implications for the correct diagnosis and treatment of these unfortunate patients is discussed.

2. Report of a Case

2.1 Clinicopathological Findings at Diagnosis

A 26 year old man presented with a dry cough, fatigue, dyspnea, decreased appetite, weight loss and night sweats in summer. His past medical history was significant for gynecomastia as a child, and azoospermia. At an outside institution, a mediastinal biopsy was performed which showed a malignant non seminomatous-GCT with embryonal, yolk sac, and teratomatous elements. The tumor was positive for AFP and HCG with focal cartilaginous differentiation and extensive necrosis, with some gland-like architecture. One month after the diagnosis he was started on Bleomycin, Etoposide and Platinum for 4 cycles lasting four months. Despite chemotherapy, he had residual disease and presented to our Institution late in the year for a left thoracotomy with
resection of the anterior mediastinal GCT and wedge resection of left upper lobe of lung. Three months following surgery the patient demonstrated progressive, unresectable disease. Biopsies demonstrated poorly differentiated malignant neoplasm, consistent with malignant sarcomatous transformation of a germ cell neoplasm.

2.2 Hematological Findings One Year Later

One year after initial diagnosis there was a precipitous drop in platelet count and a bone marrow biopsy was performed (Figure 1). The marrow was hypercellular (Figure 1A) with erythroid and myeloid atypia (Figures 1C, 1D), and myeloid left shift (Figures 1B, 1D). The marrow also showed atypical immature monocytes but CD34 immunostaining did not demonstrate increase in blasts (not shown). Extensive immunohistochemical staining, including alpha-fetoprotein (AFP), human chorionic gonadotropin (HCG), failed to reveal any germ cell antigens in the bone marrow cells (not shown). These findings suggested the diagnosis of a myelodysplastic syndrome (MDS), namely Refractory Cytopenia with Multilineage Dysplasia (RCMD). Karyotyping of the marrow showed near tetraploidy (Figure 2A). The isochromosome 12p abnormality, characteristically associated with testicular germ cell tumors and some non-gonadal GCTs was not detected. The significance of this cytogenetic abnormality for a diagnosis of MDS was not clear at the time. The patient received supportive care with transfusions.

![Figure 1. Bone marrow findings, one year after initial diagnosis of GCT](image)

Bone marrow core biopsy and aspirate. Bone marrow was obtained to investigate the severe thrombocytopenia which developed 1 year after the diagnosis of mediastinal GCT. A, B: The core biopsy is hypercellular with a cellularity of 90%, and M:E ratio of 4:1. Small clusters of immature myeloid precursors are present away from the bony trabeculae consistent with atypical localization of immature myeloid precursors (ALIPS). (H&E). C, D:
Aspirate smears demonstrate erythroid and myeloid atypia. Erythroid precursors demonstrate occasional budding and megaloblastic/megaloblastoid change. Myeloid precursors demonstrate mild nuclear and cytoplasmic asynchrony.

2.3 Terminal Events and Autopsy Findings

One month later he presented to an outside hospital with acute shortness of breath and hypoxia, and was intubated and transferred to our hospital. His condition worsened and he died three days later. The autopsy demonstrated a mediastinal NS-GCT involving the anterior chest wall with extension through the ribs into the left lung (Figures 3A, 3B, 3C). FISH was performed on the bone marrow obtained ante-mortem and the postmortem anterior chest wall mass. The marrow showed presence of multiple copies of chromosome 5, 7, 8, and 20 in 50 to 92% cells (Figures 2B, 2C, 2D) and the chest wall tumor showed the same chromosomal abnormalities as the bone marrow (Figures 3D, 3E, 3F). The bone marrow at autopsy (Figure 3) showed hypercellularity (3A) and increased immature cells (3B-3C), consistent with acute leukemia. To confirm the clonal relatedness, additional FISH was performed on the anterior mediastinal mass biopsy from the original diagnostic tissue prior to any treatment. The mediastinal biopsy showed multiple copies of chromosome 8 (3-8 copies total) in 68% of nuclei examined (not shown), similar to the ante-mortem bone marrow and postmortem chest wall mass.
Figure 3. The recurrent and refractory chest wall tumor at autopsy

A, B: Sarcomatous differentiation of tumor (H&E). C: Tumor cells show staining for alpha fetoprotein (AFP), as in the original tumor. D-F: Interphase FISH performed on paraffin sections of the tumor for chromosomes 5, 7 and 8 show four copies of each chromosome in almost all cells.
3. Discussion

3.1 Therapy induced Myeloid Neoplasm—Typical Time Course and Cytogenetics

This case illustrates a potential diagnostic pitfall arising in patients with mediastinal-GCT. The peripheral blood cytopenia(s) and cytological dysplasia in the hematopoietic precursors seen in these patients mimic a therapy related myeloid neoplasm. It is assumed that the combination of cytopenia and myeloid dysplasia detected in a patient previously treated with chemotherapy and/or radiation therapy indicates the development of therapy related MDS/AML (Vardiman et al., 2008). The time course of development of these secondary hematological changes is largely dependent on the nature of the chemotherapeutic agent used (Leone, Fianchi, Pagano, & Voso, 2010). Prior therapy with alkylating agents, which damage DNA either by methylation or DNA inter-strand crosslink formation, typically cause hematologic neoplasm in five to seven years. A distinct phase of MDS precedes the development of AML. In contrast, treatment with DNA-topoisomerase II inhibitors, which bind to the enzyme/DNA complex at the strand cleavage stage and block the enzymatic reaction of re-ligation causing permanent strand break in the DNA, have a shorter latency of 1 to 3 years. These patients develop AML without a preceding phase of MDS. The presentation in our patient was within a year of chemotherapy and initially blasts were not increased. This time course is not typical for therapy related MDS/AML (Vardiman et al., 2008). In our patient the karyotyping of the marrow showed near tetraploidy (Fig 2L) and FISH confirmed presence of...
multiple copies of chromosome 5, 7, 8, and 20 in 50 to 92% cells. We also demonstrated the multiple copies of 8 in the anterior mediastinal mass prior to treatment, which removes treatment as a cause for the hyperdiploidy. In therapy induced MDS, monosomy of chromosome(s) 7 and/or 5 or deletion of their long arm are most commonly observed in patients with prior alkylating agent therapy. Balanced translocations involving chromosome bands 11q23 and 21q22 are usually associated with topoisomerase II inhibitor therapy (Leone et al., 2010; Vardiman et al., 2008). A hypodiploid pattern is also not uncommon in these cases (Whang-Peng et al., 1988) but hyperdiploidy appears to be rare and when present should raise suspicion for an alternate diagnosis.

3.2 Association between Mediastinal GCT and Hematological Abnormalities – Historical Perspective

The association between mediastinal -GCT and hematological abnormalities was first recognized almost three decades ago (Garnick & Griffin, 1983) in three patients who developed severe idiopathic thrombocytopenia unresponsive to steroids and splenectomy. Hematological malignancy was not diagnosed at that time, but in retrospect, the increased megakaryocytes in these cases may have been an indication of MDS. Subsequently several cases of secondary hematologic malignancies developing in patients with mediastinal nS-GCTs have been reported. One of the earliest reports was by Nichols et al. (1985) who described three men with primary mediastinal germ-cell tumors who developed a malignant hematologic disorder: acute megakaryocytic leukemia in two and myelodysplastic syndrome with a prominent megakaryocytic component in the third patient. Because both mediastinal-GCT and acute megakaryocytic leukemia are rare conditions, the authors believed that their concurrent occurrence was highly unlikely to be merely a coincidence. Moreover, based on the short interval since prior chemotherapy, they argued against a treatment related secondary hematological malignancy. They postulated that the clinical syndrome of mediastinal GCT and hematopoietic neoplasm represents an intrinsic biologic link between the primordial germ cells and hematopoietic stem cell. They pointed out the topographical relatedness between primordial germ cells and hematopoietic stem cells during embryological development. The recent developments in our understanding of embryological development of germ cells and hematological stem cells (Baron, Isern, & Fraser, 2012) does not fundamentally alter the intimate relationship between these cell types. Clonal identity between the two malignancies was not considered likely or proven in their three cases or in the 13 cases they collected from the literature at that time. Three cases (one seen by the authors and two from their literature review) had cytogenetic information available and all showed the +8 abnormality. This suggested that these were likely de-novo acute myeloid leukemia rather than therapy induced leukemia, an argument supported by the prompt and lasting remission obtained in their patient with this abnormality.

3.3 Cytogenetic Evidence of Clonal Relationship between GCT and Hematological Malignancy

Clonal relatedness between the mediastinal GCT and hematopoietic neoplasm was first demonstrated by serial cytogenetic examination and the recognition of i(12p) abnormality in both neoplasms (Chaganti et al., 1989). It is now well established that i(12p) is a characteristic and nearly invariable cytogenetic abnormality in testicular germ cell tumors, both seminomas and non-seminomas, occurring in adolescents and young adults (Looijenga et al., 2003). It may be seen in few cases of extra-gonadal GCTs, but this or any other cytogenetic abnormality is not considered characteristic for extra-gonadal GCT (Nichols, Roth, Heerema, Griepp, & Tricot, 1990). Subsequently additional cases of hematological malignancy associated with mediastinal germ cell tumors have been shown to contain the I (12p) abnormality (Ikdahl et al., 2008; Vlasveld, Splinter, Hagemeijer, Van Lom, & Lowenberg, 1994; Woodruff et al., 1995; Yu, Kim, Cha, Park, & Kim, 2011), often along with +8 or other complex cytogenetic abnormalities. A recent review of published cases found about 65 reported cases of hematological abnormalities associated with mediastinal GCT (Yu et al., 2011) and some of them occur concurrently with the diagnosis of GCT (Ikdahl et al., 2008). Many cases of hematological malignancy associated with mediastinal GCT are of uncommon subtypes such as acute megakaryoblastic leukemia and it has been suggested that the detection of such neoplasms in young adult males should prompt a search for mediastinal GCT (Ikdahl et al., 2008). Besides i(12p), Kleinfelter’s syndrome is 30 to 40 times more common in patients with mediastinal GCT than the general population (Lachman, Kim, & Koo, 1986). A patient with Kleneftel’s syndrome who developed a mediastinal immature teratoma with yolk sac elements and a myelomonocytic leukemia was described (Govender & Pillay, 2002). Our patient had gynecomastia as a child, and had been in the process of being worked up for azoosperma, which raises a suspicion for Kleinfelter’s syndrome, but somatic karyotyping was not carried out.

3.4 Developmental Biology and Pathobiology Connecting Mediastinal GCT and Hematological Neoplasms

A retrospective analysis of multicenter data from USA and Europe over a 21 year period suggests that hematological abnormalities occurring early in the course of GCT are almost always encountered in patients with a mediastinal location of the GCT (Hartmann et al., 2000). This nearly constant association suggests a
fundamental biological link between the two processes, as suggested originally by Nichols (Nichols et al., 1985). While metastasis of NSGCT to the bone marrow are rare, with only a few case reports available in the literature (Chandra et al., 2002; Orduz et al., 2005), it is interesting that these cases are of mediastinal origin. Embryologically, early hematopoiesis occurs in the aorta-gonad-mesonephros region, very shortly after the earliest hematopoiesis seen in the yolk sac (Baron et al., 2012). The mediastinum may contain rests of primitive germ cells and hematopoietic stem cells. Either both type of cells may undergo malignant transformation or the transformed pluripotent germ cell itself may transdifferentiate into hematopoietic cells under the influence of environmental signals, such as those from the bone marrow stromal cells (Wang, Zhang, Liu, & Zou, 2012). The finding of identical cytogenetic abnormalities in the GCT and hematological neoplasm support their origin from the same clone, but this is demonstrated only in a small minority of published cases (Nichols et al., 1985; Nichols et al., 1990). It is noteworthy that, similar to our patient, almost all hematological neoplasms seen in patients with mediastinal GCT involve only those sites which commonly show hematopoiesis under physiological or pathological conditions in adults, that is the bone marrow and spleen, while the mediastinal tumor continues to show GCT morphology (embryonal carcinoma, yolk sac tumor etc). Even during recurrence and tumor progression these site specific morphological and immunophenotypic characteristics remain (Fig 1 and 2). This may explain why bone marrow metastasis of NSGCT, which are identifiable as such are rare, either at primary diagnosis (Chandra et al., 2002; Orduz et al., 2005) or during recurrence (Garbay et al., 2012). Presumably the tumor cells tend to transdifferentiate into hematopoietic elements in this site. These observations suggest a central role for the bone marrow stromal cells in hematopoietic differentiation of pluripotent malignant cells of the GCT. Furthermore, these abnormal hematopoietic precursors transdifferentiated from the GCT appear to suppress normal hematopoiesis as shown by the high proportion of marrow cells with cytogenetic abnormalities by FISH (Fig 1H). As tumor progression occurs, the bone marrow disease may transform into acute myeloid leukemia from the original myelodysplastic syndrome, but does not de-differentiate to GCT.

3.5 Prognosis and Treatment Choice

In most patients with a hematological malignancy developing along with a mediastinal GCT, the prognosis is quite dismal (Ikdhahl et al., 2008). This may reflect the innate property of a GCT which has the capacity to trans-differentiate into hematopoietic cells, but may also indicate the adverse impact of a clonally independent but concurrent malignancy. It should be noted that at least some patients may have a sustained response to chemotherapy directed to the hematological neoplasm (Nichols et al., 1985). Whether all patients of mediastinal GCT who develop a hematological malignancy should receive specific chemotherapy for the hematological condition is not clear. It may be suggested from available data, that demonstration of clonal identity between the GCT and hematological malignancy would portend a grave prognosis, irrespective of treatment, including aggressive surgical treatment of the mediastinal tumor itself. Without a clearly demonstrated clonal identity between the two processes, and when the hematological neoplastic cells contain cytogenetic abnormalities such as +8, chemotherapy directed at these neoplasms may have a role in managing these patients.

4. Conclusion

There is an infrequent but characteristic association between mediastinal GCT and hematological neoplasia, possibly a result of close embryological relatedness of cells giving rise to mediastinal (but not gonadal) GCT and hematological stem cells. Most of these patients carry a dismal prognosis. Appropriateness of aggressive therapy for the GCT itself and the need for separate chemotherapy for the hematopoietic malignancy needs additional study.

References


