Hematologic Disorders Associated With Primary Mediastinal Nonseminomatous Germ Cell Tumors

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Background. The association between primary germ cell tumors of the mediastinum (the space between the lung pleura that contains the heart and other chest viscera) and hematologic malignancies has been described by retrospective analysis of patients treated at individual clinical centers. To better characterize the risk of hematologic disorders in patients with extragonadal germ cell tumors and to describe the clinical and biologic features of the disorders, we studied an unselected population in a large, international, multicenter database. Methods. Six hundred thirty-five patients treated at 11 centers in the United States and Europe from 1975 through 1996 were evaluated retrospectively. Results. A hematologic disorder was observed in 17 patients with germ cell tumors. All cases developed among the 287 patients with primary mediastinal nonseminomatous germ cell tumors, giving an incidence rate of 2.0% (95% confidence interval [CI] = 1.1%–3.1%) per year over a median follow-up time of 3 years. The risk of developing hematologic disorders was statistically significantly increased in patients with primary mediastinal nonseminomatous germ cell tumors in comparison with the age-matched general population (standardized incidence ratio = 250; 95% CI = 140–405). The median time to onset of hematologic neoplasia was 6 months (range, 0–47 months), and the median survival after diagnosis of the hematologic disorder was 5 months (range, 0–16 months) (two-sided \[P<0.001\], comparing survival from the time of diagnosis of the germ cell tumor of patients with and without hematologic disorders). Conclusion. In our study, approximately one in 17 patients with primary mediastinal nonseminomatous germ cell tumors was affected by a hematologic disorder, whereas no cases were seen among 334 patients with other extragonadal germ cell tumors. The hematologic disorder had a statistically significant impact on prognosis, with none of the 17 reported patients surviving for more than 2 years. [J Natl Cancer Inst 2000;92:54–61]

Hematologic neoplasias associated with extragonadal germ cell tumors represent one of the most intriguing and biologically distinctive aspects of male germ cell cancers. Since the association was first recognized in 1985, a small number of cases have been reported (1,2). Patients affected with hematologic malignancies presented with a germ cell tumor located in the mediastinum, each with a nonseminomatous histology. Teratocarcinoma and endodermal sinus tumors had been noted in the majority of patients. The largest series, with 16 patients, reported a median time interval of 6 months (range, 0–122 months) from the diagnosis of mediastinal germ cell tumor to the occurrence of a hematologic disorder (3). Approximately one third of patients presented with both disorders simultaneously. Most often, the megakaryocytic lineage of hematopoesis was involved in the hematologic malignancy, resulting in acute megakaryoblastic leukemia, myelodysplasia with abnormal megakaryocytes, or idiopathic/essential thrombocytosis. Other hematologic diagnoses included acute lymphocytic or other acute myeloid leukemia (AML) and, in rare cases, malignant histiocytosis or systemic mastocytosis (3–7).

Hematologic disorders associated with primary mediastinal germ cell tumors have to be distinguished from therapy-related secondary leukemia. Leukemias associated with the use of alkylating agents usually occur after an interval of 5–7 years, often preceded by a preleukemic period of myelodysplasia and frequently progressing to AML, French–American–British classification (FAB) subtypes M1 or M2 (8). Topoisomerase II inhibitor-related secondary leukemias are generally diagnosed 2–3 years after chemotherapy and most commonly exhibit FAB M4 or M5 phenotype. Whereas the latter type of leukemias is frequently associated with translocations of the long arm of chromosome 11 (11q23) (9–12), the leukemias following treatment with alkylating agent-containing regimens displayed alterations in chromosome 5 or 7 in a high proportion of patients (60%–90%). In contrast, leukemias associated with mediastinal germ cell tumors appeared to have no consistent cytogenetic abnormalities (3). However, the typical marker chromosome abnormality of testicular cancer, isochromosome i(12p), had been identified within leukemic blasts in some cases, indicating a biologic relationship between testicular cancer and leukemia in other cases. Other cytogenetic findings in leukemic blasts, such as evidence of XXY or trisomy 21 karyotypes, may be related to the rare but documented association of mediastinal germ cell tumor and Klinefelter’s syndrome or Down syndrome (13,14).

The clinical course of the hematologic neoplasia in patients with germ cell tumors tends to be very aggressive, and a substantial proportion of these patients die before treatment. Patients have either not responded to antileukemic treatment or attained only brief remissions. A subgroup of patients with isolated thrombocytosis/platelet disorders appears to have a more favorable prognosis (4,5).

Only limited data are available regarding the frequency, clinical behavior, and biology of hematologic neoplasias in patients with primary mediastinal germ cell tumors. This investigation adds information from a large database containing information on patients with extragonadal germ cell tumors from 11 European and American cancer centers. The patients were treated during a recent time period when cisplatin-based chemotherapy regimens were generally available.

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PATIENTS AND METHODS

Data Collection

We evaluated the medical records of 635 extragonadal germ cell tumor patients treated at 11 cancer centers in the United States and Europe during the period from 1975 through 1996. The contributing centers, internationally recognized for their experience in the treatment of germ cell tumors, were as follows: Indiana University, Indianapolis (n = 216; time period, 1989 through 1996); Institute Gustave-Roussy, Villejuif, France, Centre Léon-Berard, Lyon, France, and the Groupe d’Etude des Tumeurs Uro-geniales, Lyon (n = 93 from these three centers; time period, 1975 through 1996); Eberhard-Karls-University Medical Center II, Tuebingen, Germany (n = 13; time period, 1986 through 1993); Hanover University Medical School, Germany (n = 88; time period, 1978 through 1995); The Norwegian Radium Hospital, Oslo (n = 48; time period, 1980 through 1995); Klinikum Großhadern, Munich, Germany (n = 63; time period, 1979 through 1996); The Royal Marsden Hospital, Sutton, U.K. (n = 65; time period, 1979 through 1994); Kaiser-Franz-Josef Spital, Vienna, Austria (n = 19; time period, 1975 through 1996); and Virchow-Klinikum, Berlin, Germany (n = 30; time period, 1987 through 1994). The reason for referral of patients to each center was the diagnosis of extragonadal germ cell tumor. For data collection, a standardized questionnaire was sent to each center and completed by the responsible co-investigator. All patients’ data were obtained in an anonymous manner; because chart review was done anonymously and retrospectively, no institutional approval was necessary at any of the participating institutions. Detailed information on patients’ characteristics, such as (a) location and histology of primary tumor, (b) extent of disease, including serum tumor marker concentrations of β-human chorionic gonadotropin (β-HCG), α-fetoprotein (AFP), and lactate dehydrogenase (LDH), (c) history of testicular abnormalities, (d) details on diagnostic methods, treatment, response to treatment, and follow-up period, and (e) data on secondary testicular cancer and other secondary cancers, was acquired. The completed questionnaires were checked for plausibility and data consistency at Tuebingen University Medical Center. When important data were missing, the questionnaires were returned to the principal investigator at each center. In addition, charts of 229 patients (36%) were re-abstracted by the principal investigator. For this report, the clinical records of patients who developed a hematologic malignancy associated with an extragonadal germ cell tumor were reviewed in detail. All histopathologic slides of these cases were reviewed by each center’s hematopathologist.

Tumor response and disease remission were defined as follows: Complete remission (CR) was defined as a complete disappearance of all clinical, radiologic, and biochemical evidence of disease. A partial response with marker normalization (PRm–) was defined as any decrease in tumor size and normalization of all elevated tumor markers. PR without marker normalization (PRm+) was defined as a radiologic response greater than 50% in size but no complete normalization of β-HCG and/or AFP and/or LDH after completion of chemotherapy. Progressive disease was defined as either an increase in the size of residual lesions or the occurrence of new lesions and/or elevation of tumor markers at repeated controls (15).

Statistical Analysis

The duration of follow-up was calculated on the basis of the date of the diagnosis of the extragonadal germ cell tumor until the date of last contact (if the patient was still alive) or the date of death. For all living patients, the current status as of August 1998 was verified. Survival calculations in this analysis were performed both from the diagnosis of the hematologic disorder and from the evidence of extragonadal germ cell tumor. To determine the number of new cases of leukemia expected in the study group, we used 5-year age group-specific data from the cancer registry of the Federal state of Saarland, located in southwest Germany, from 1975 through 1996. This cancer registry is a population-based registry that covers the state of Saarland. The types of leukemia reported and included in the calculation were lymphoid, myeloid, monocytic, and unclassified/other leukemias. The results were standardized on the basis of age and duration of follow-up (patients’ years of risk) and were expressed with the use of the standardized incidence ratio (SIR) with the associated 95% confidence interval (CI) calculated on the assumption of a Poisson distribution (16). The SIR was considered statistically significant if the 95% CI did not include the value 1.0. The SIR was calculated with the use of the SAS system (SAS 6.11 for Windows; SAS Institute, Inc., Cary, NC). A SAS macro (programmed and available at the Institute for Medical Information Processing, University of Tuebingen) and PROC UNIVARIATE were used to calculate the patients’ years at risk, the expected number of cases for every age group, and the SIR according to the procedure described by Breslow and Day (16). The two patients who presented simultaneously with both diseases—germ cell tumor and associated leukemia—were not included in the SIR calculation. The rationale for the use of the age group-specific data available from the Saarland Cancer Registry was that this procedure considered the changes in the incidences of leukemias during the period of approximately 20 years. Despite some differences between the countries included in the analysis, the incidence rates are comparable. Differences in rates among the participating countries are smaller than those among different cancer registries within single countries, particularly when age and time period-specific data are being considered (17). In addition, the proportion of patients developing hematologic disorders in the 1st, 2nd, and 3rd years after diagnosis of extragonadal germ cell tumors was calculated as follows: 

\[
\text{in year 1} = \frac{\text{No. of new cases}}{\text{All patients} - \left( \frac{\text{No. of germ cell tumor deaths} + \text{No. of new cases}}{2} \right)}
\]

\[
\text{in years 2 and 3} = \frac{\text{No. of new cases}}{\text{All patients} - \left( \frac{\text{No. of germ cell tumor deaths} + \text{No. of new cases}}{2} \right) + \text{No. still alive with leukemia} + \text{No. of prior deaths}}
\]

All other statistical analyses were performed with the use of the SPSS system (SPSS for Windows 8.0 software; Microsoft Corp., Redmond, WA) according to the Kaplan–Meier method to calculate survival data (18). A multivariable logistic regression including all 287 patients with primary mediastinal germ cell tumors was performed to identify patients’ characteristics predicting the occurrence of leukemia in association with primary mediastinal germ cell tumor (19). The following categorical variables were examined: histologic subgroups of the primary tumor (yolk sac/teratocarcinoma/other), age grouping (<25 years old and ≥26 years old), tumor marker concentrations at diagnosis (elevated, yes/no), size (<25 cm² and ≥26 cm²) and presence of additional metastatic sites (yes/no), medical history (Klinefelter’s syndrome, yes/no), and type of chemotherapy (etoposide, yes/no). Continuous variables were age and tumor marker concentrations of LDH, β-HCG, and AFP at diagnosis. All reported P values were two-sided.

RESULTS

In total, 635 patients (median age, 30 years; range, 14–79 years) were included in the analysis; 341 patients (54%) had a primary mediastinal tumor, 283 (45%) had a retroperitoneal germ cell tumor, one patient (0.2%) had cervical lymph node involvement, and 10 patients (1.6%) had no primary tumor. Of the patients with mediastinal localization, 287 (84%) had a tumor of nonseminomatous histology, 51 patients (15%) had a seminomatous mediastinal tumor, and three patients had a tumor of undetermined histology.

Overall, 17 patients with hematologic disorders were identified in the whole dataset of 635 patients. The median age at diagnosis of the germ cell tumor was 23 years (range, 17–35 years). All of the patients with hematologic malignancies had the diagnosis of a primary nonseminomatous mediastinal germ cell tumor. The histologic findings included teratocarcinoma in 10 patients (59%), endodermal sinus tumor in four patients (24%), and an undifferentiated germ cell tumor in one patient (6%). Two patients (12%) had only a serologic diagnosis based on tumor marker concentrations (elevated serum...
AFP and/or β-HCG), with a gross diagnosis of mediastinal tumor (Table 1). None of the 283 patients with retroperitoneal germ cell tumors and none of the 51 patients with mediastinal seminoma registered in the database developed a hematologic disorder. Serum concentrations of the tumor markers AFP, β-HCG, and LDH were elevated in 82%, 41%, and 47% of the 17 patients, respectively. All of the patients had received cisplatin-based combination chemotherapy. One complete remission and 10 partial remissions with marker normalization were observed, resulting in an overall response rate of 64.7% (95% CI = 41.3%–88.1%). All of the patients with partial remissions underwent secondary resection of their primary tumor. Of the remaining six patients, four did not achieve a normalization of any or all of the tumor markers and two other patients had a rapid progression of the hematologic disorder that occurred simultaneously and, therefore, responsive to germ cell tumor-related therapy was not determined.

The median time from the diagnosis of the primary mediastinal germ cell tumor to the diagnosis of the hematologic neoplasm was 6 months (range, 0–47 months) (Table 2). Hematologic neoplasms within 1 year of the diagnosis of the germ cell tumor occurred in 11 (65%) of the 17 patients. Two patients (12%) presented with a simultaneous onset of both disorders. The hematologic disorders were characterized as acute megakaryoblastic leukemia (FAB M7) in five patients, myelodysplasia with abnormal megakaryocyte in five patients, acute undifferentiated leukemia and malignant mastocytosis in two patients each, and acute myeloblastic leukemia (FAB M2), acute myelomonocytic leukemia (FAB M4), and malignant histiocytosis in one patient each.

Cytogenetic analyses were available for 13 of 17 patients (Table 2). No consistent chromosomal abnormality was identified. However, in five (38%) of 13 patients, the germ cell tumor marker chromosome i(12p) was found. Other karyotypic abnormalities included trisomy 8 in two (15%) of 13 patients and the karyotype of Klinefelter’s syndrome (XYY) in one patient (8%). Six patients (46%) had normal karyotypes.

Seven (41%) of 17 patients did not receive any therapy for their hematologic disorder because of its fulminating clinical course. Eight patients with acute nonlymphocytic leukemia were treated with combination chemotherapy based on cytarabine/anthracyclines, resulting in only one short remission. Two other patients underwent allogeneic bone marrow transplantation without success: One of them had an early relapse, and the other died of treatment-related toxic side effects. Both patients with malignant mastocytosis received only treatment of their symptoms with steroids and histamine receptor antagonists (data on treatment not shown).

The most common clinical features at the diagnosis of the hematologic disorder included pancytopenia (n = 6), organomegaly (i.e., splenomegaly and hepatomegaly) (n = 5), particularly splenomegaly, or isolated thrombocytopenia (n = 4) (Table 3). All patients with acute megakaryoblastic leukemia presented with pancytopenia and, in addition, three of five had organomegaly and/or circulating leukemic blasts (n = 2). In patients with myelodysplasia with abnormal megakaryocytes, patients presented either with pancytopenia or with isolated thrombocytopenia. The two patients with malignant mastocytosis showed symptoms associated with increased histamine production, such as flushing, exanthema, and bronchospasm.

In the examination of bone marrow aspirates, all of the patients with acute megakaryoblastic leukemia revealed a diffuse infiltration with megakaryocytes blasts (Table 3). The most common finding in patients with myelodysplastic syn-

Table 1. Characteristics of 17 patients with nonseminomatous mediastinal germ cell tumors and hematologic disorders*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>17 (100%)</th>
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<th>1 (6%)</th>
<th>2 (12%)</th>
<th>6 (47%)</th>
<th>10 (59%)</th>
<th>1 (6%)</th>
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<tr>
<td>Anatomic localization of primary tumor</td>
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<tr>
<td>Histology: nonseminomatous GCT</td>
<td>Teratocarcinoma</td>
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<td>Elevated serum tumor markers</td>
<td>α-Fetoprotein</td>
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<tr>
<td>Human chorionic gonadotropin</td>
<td>14 (82%)</td>
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<td>Lactate dehydrogenase</td>
<td>5830 (1 to 64 000)</td>
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<td>Median (range) in IU/L</td>
<td>7 (41%)</td>
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<tr>
<td>Treatment for GCT</td>
<td>PEB</td>
<td>PEB</td>
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<tr>
<td>Response to treatment for GCT</td>
<td>Complete remission</td>
<td>Complete remission</td>
<td>Complete remission</td>
<td>Complete remission</td>
<td>Complete remission</td>
<td>Complete remission</td>
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*GCT = germ cell tumor; n.e. = not evaluable because of rapid progression of the hematologic disorder; PEB = cisplatin, etoposide, bleomycin; PV = cisplatin, vinblastine, bleomycin; PEI = cisplatin, etoposide, ifosfamide; PVEBV = cisplatin, etoposide, bleomycin, vinblastine; BOP/VIP = bleomycin, vincristine, cisplatin, etoposide, ifosfamide; CISCA/VB = cisplatin, cyclophosphamide, doxorubicin, vinblastine, bleomycin; C–BOP = carboplatin, cisplatin, bleomycin.
†Patients had a mediastinal mass without histologic diagnosis of the tumor and elevation of tumor marker concentrations (Table 3). All patients with acute myeloblastic leukemia presented with pancytopenia and, in addition, three of five had organomegaly and/or circulating leukemic blasts (n = 2). In patients with myelodysplasia with abnormal megakaryocytes, patients presented either with pancytopenia or with isolated thrombocytopenia. The two patients with malignant mastocytosis showed symptoms associated with increased histamine production, such as flushing, exanthema, and bronchospasm.

In the examination of bone marrow aspirates, all of the patients with acute megakaryoblastic leukemia revealed a diffuse infiltration with megakaryocytes blasts (Table 3). The most common finding in patients with myelodysplastic syn-
dromes was an increased number of abnormal megakaryocytes or an excess of blast cells. Aspirates of patients with myelodysplastic syndromes revealed either an increased cellularity or a hypocellular marrow with a marked dysplasia of the erythrocyte lineage (Table 3).

All 17 patients died within 2 years after diagnosis of their hematologic neoplasia, resulting in a median survival time of 5 months (range, 0–16 months). The median survival from the time of the diagnosis of extragonadal germ cell tumors was 14 months (range, 4–52 months; 95% CI = 8.6–21.4 months) for those who developed hematologic disorders compared with 51 months (range, 0–178+ months; 95% CI = 0–106+ months) for germ cell tumor patients who did not develop hematologic neoplasia (P<.0001) (Fig. 1).

The proportion of patients developing hematologic neoplasia associated with mediastinal germ cell tumors of nonsemionomatous differentiation after a median follow-up of 32 months (95% CI = 1–63 months) was 5.9% (17 of 287; 95% CI = 3.5%–9.3%), corresponding to an incidence rate of 2.0% (95% CI = 1.1%–3.1%) per year. This difference is highly statistically significant, as indicated by the 95% CI.

The proportion of patients developing hematologic disorders was highest in the first year (4.8% in the first 12 months) after the diagnosis of mediastinal nonseminomatous germ cell tumor, decreasing to 1.5% and to 0.6% during the 2nd and 3rd years, respectively. No further cases of secondary leukemia were observed either among the 270 patients with primary mediastinal nonseminomatous germ cell tumors or among the remaining 348 patients with extragonadal germ cell tumors during the observation period. In the logistic regression model, no particular patients' characteristics—with the exception of mediastinal germ cell tumor lo-
**DISCUSSION**

Since the original recognition of the association between hematologic disorders and primary mediastinal nonseminomatous germ cell tumor in 1985 (1,2), more than 70 cases have been described in the literature (1–3,6,20–50). Most reports have included a limited number of patients; therefore, the incidence rate of hematologic neoplasia, risk factors for the occurrence of the associated neoplasia, and the RR compared with the normal population could not be determined among patients with primary mediastinal germ cell tumors. The largest collection of cases was described by Nichols et al. (3) in 1990 in a report of 16 patients with mediastinal germ cell tumors with associated hematologic neoplasia who had been treated at two institutions in the United States from September 1983 through December 1988. From 1976 through 1988, the same authors had evaluated 31 consecutive patients with primary mediastinal germ cell tumors at Indiana University. Hematologic neoplasms developed in five (16%) of the patients with mediastinal germ cell tumors (3).

Based on our data, hematologic malignancies associated with primary mediastinal germ cell tumors are mainly disorders of the megakaryocyte lineage characterized as AML M7 (acute megakaryoblastic leukemia) and myelodysplastic syndrome with abnormal megakaryocytes. Several cases of acute lymphoblastic leukemia (3–5,38,40,41,45), malignant histiocytosis or systemic mastocytosis (6,25,23,33,44), and, rarely, monoblastic, myelomonoblastic, mixed-lineage leukemia and idiopathic or essential thrombocytosis (4,5) have also been described. In addition, a patient with a focus of non-Hodgkin’s lymphoma in the primary mediastinal tumor has been reported (39).

Cytogenetic analysis of bone marrow aspirates revealed the finding of the most common karyotypic abnormality of germ cell tumor—isochromosome i(12p)—in 38% (five of 13) of our patients compared with 35% (13 of 37) in a summary of data from the literature. Karyotypes of trisomy 8 (16%) as well as the evidence of Klinefelter’s syndrome or XXY (14%) have been observed in some patients. Other cytogenetic findings were reported infrequently. Ladanyi et al. (48) identified a series of six patients with evidence of germ cell origin of the acute leukemia. One patient had an isochromosome i(12p) in his germ cell tumor and in leukemic blasts [which were reported earlier in another patient (24)], a second patient had evidence of i(12p) in leukemic cells, and, in a third patient, the leukemic cells coexpressed myelomonocytic antigens (HAM56 [human macrophage antigen 56], My4, and My9) and cytokeratin, suggesting both myeloid and germ cell differentiation. The clonal relationship between a mediastinal germ cell tumor and acute myelogenous leukemia was supported by another case reported by Woodruff et al. (43). At presentation, their patient had a mediastinal tumor con-
sisting histologically of immature teratoma and yolk sac elements and myelodysplasia on bone marrow examination. Both the cells in the bone marrow and the mediastinal tumor had the same karyotype [49,XY; +X;+i(12p);+8]. (Note: + indicates the presence of extra copies of the indicated chromosomal material.) In addition, Orazi et al. (49) identified leukemic blasts and erythroblasts within the yolk sac component of a mediastinal germ cell tumor associated with leukemia. The leukemic cells within the mediastinal tumor expressed CD34 and other myeloid and erythroid markers, as well as p53, which was also overexpressed in the mediastinal germ cell tumor but has been reported very rarely in acute leukemias. The expression of p53 was found in another two of six patients. In addition, two of five patients with mediastinal germ cell tumor-associated leukemias showed an i(12p) isochromosome, which is usually not observed in leukemias (51). In the present series, the resected yolk sac tumor specimen of one patient had a focus of i(12p)-positive blasts.

We observed a short interval between the diagnosis of germ cell tumor and the diagnosis of the hematologic disorder. The median time was 6 months following the diagnosis of germ cell tumor. It is interesting that 10%–30% of patients observed presented with a simultaneous onset of both disorders in two investigations [current series; (3)].

The hematologic neoplasms associated with primary mediastinal germ cell tumors possess a very aggressive clinical course; patients either die before treatment, do not respond to antileukemic therapy, or achieve only short remissions. Allogeneic bone marrow transplantation may be the only curative strategy, despite our experience with two patients who failed to respond to this treatment. However, a subgroup of patients with platelet disorders seemed to have a slightly better prognosis (4,5). The observed survival reported in the literature ranges from 1 month up to 6 months in accordance with the present series, demonstrating a median survival time of 5 months (range, 0–16 months).

The development of leukemia in patients with nonseminomatous extragonadal germ cell tumors clearly affects the prognosis. While approximately 50% of patients with nonseminomatous mediastinal germ cell cancers registered in our database are long-term survivors following cisplatin-based chemotherpay, none of the patients with an additional hematologic disorder is alive at 5 years after diagnosis (Fig. 1). Our analysis clearly confirms that the risk for developing hematologic disorder among patients with germ cell tumors affects only those whose primary mediastinal germ cell tumor has a nonseminomatous histology. Based on the large database containing patients from 11 centers worldwide, the incidence of leukemia in patients with mediastinal nonseminomatous germ cell tumors is estimated to be 5.9% (95% CI = 3.5%–9.3%) and is, therefore, clearly lower than an earlier estimate of 16% based on a nonrepresentative cohort of patients with extragonadal germ cell tumor (3). Thus, approximately one in 17 patients will be affected by this association. The risk of developing a germ cell tumor-related leukemia was highest during the 1st year after the diagnosis of a mediastinal germ cell tumor, with 12 (71%) of 17 cases occurring in this time interval in the present series. The proportion of patients developing germ cell tumor-related leukemia decreased from 4.8% in the first 12 months to 1.5% and 0.6% during the 2nd and 3rd years, respectively, after the diagnosis of mediastinal nonseminomatous germ cell tumor. However, rare cases of late onset of the hematologic disease have been reported. The latest case has been described in the literature 102 months after the diagnosis of mediastinal germ cell tumor (3).

No specific clinical or biologic variable could be identified to predict the subsequent occurrence of a leukemia, with the exception of mediastinal germ cell tumor localization and the histology of endodermal sinus tumor and teratocarcinoma. It remains unclear why some patients with nonseminomatous mediastinal germ cell tumor develop a hematologic disorder, whereas the majority of patients are unaffected. Clearly, based on the cytogenetic findings—i.e., high incidence of i(12p)—and the short time before their diagnosis, no relationship exists between the treatment of germ cell tumor and the development of leukemia. The cytogenetic and molecular biologic findings (48,49) imply that the hematologic malignancy and the mediastinal germ cell tumor arise from a common progenitor cell. Mediastinal germ cell tumors show different clinicopathologic features from gonadal and retroperitoneal germ cell tumors. They often contain areas of yolk sac tumor that have a mesenchyme-like pluripotent component. These areas may be the location at which germ cell tumors are transformed into malignancies typical of nongerminal tissues—sarcomas, most frequently (52). This suggestion is supported by the reported observation by Orazi et al. (49) that the leukemic cells of mediastinal germ cell tumors occurred predominantly in the vascular structures of the mesenchyme-like component. In addition, teratoma containing all three germ layers with varying degrees of differentiation is derived from a malignant precursor cell, embryonal carcinoma or yolk sac tumor. These precursor cells are totipotential—i.e., they are able to differentiate into different nongerminal tissues—and malignant transformation of such cells has been observed frequently (39). In addition, teratocarcinoma cells have been shown to differentiate along hematopoietic lineages in vitro and to form hematopoietic tissue in mosaic mice (53,54). Thus, most reported cases of hematologic disorders have been in mediastinal teratocarcinoma [(3); current series]. The immunohistochemical and cytogenetic findings of the early progenitor marker CD34, p53 overexpression, and particularly the evidence of trisomy 8—which was found in two of our patients—suggest some accordance to other stem cell disorders like chronic granulocytic leukemia and myeloproliferative disorders (e.g., polycythemia vera and metaplasia of unknown origin). Trisomy 8 (in combination with overexpression of p53) has been identified as being responsible for the acute transformation of chronic granulocytic leukemia (55). This finding is consistent with the coexistence of differentiated hematopoiesis and foci of acute leukemia within the same mediastinal germ cell tumor and provides evidence for a multistep hematologic transformation. The accumulation of blast cells within the tumor blood vessels supports the hypothesis of a subsequent population in the bone marrow, spleen, or liver, which recapitulates the normal embryonal dissemination of hematopoietic elements from the embryonal yolk sac into the hematopoietic sites (56). This appears to be the same pathologic mechanism described in myelofibrosis with myeloid metaplasia or, in the case of metastatic carcinoma with marrow involvement, where hematopoietic stem cells populate the fetal sites of blood production—spleen and liver—to restore he-
matopoiesis when bone marrow is insufficient.

Both extended insights into the biology of this disease association and improved strategies to treat hematologic disorders in primary mediastinal nonsemionomatous germ cell tumors should be areas of further investigation.

REFERENCES


NOTES

Elevation of AFP and/or β-HCG with evidence of a mediastinal mass is considered specific for the diagnosis of extragonadal nonseminomatous germ cell tumor. Tumor markers allow discrimination between nonseminomatous germ cell tumor (elevation of β-HCG and AFP) and other mediastinal tumors, including seminomatous germ cell tumor (no elevated markers).

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