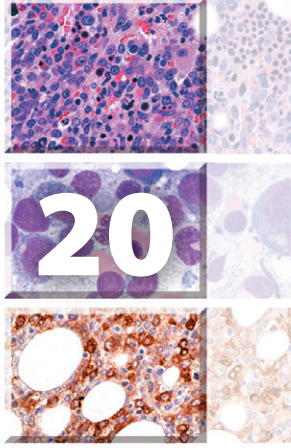

Therapy-Related Myeloid Neoplasms

Therapy-related myeloid neoplasms (t-MN) represent a spectrum of progressive clonal myelogenous disorders which are evolved following cytotoxic chemotherapy and/or irradiation. These include therapy-related AML (t-AML), therapy-related MDS (t-MDS), and therapy-related MDS/MPN (t-MDS/MPN). The reason for chemotherapy or irradiation is usually a primary malignancy. However, approximately 5% of patients with t-MPN have no prior malignancy and undergo cytotoxic chemotherapy for autoimmune disorders.

The latency period between the initiation of chemotherapy and/or irradiation and the development of t-MPN ranges from several months to several years. Overall, the latency period is shorter in patients treated with topoisomerase II inhibitors than in those treated with alkylating agents or radiation, and longer in younger patients and patients with a non-malignant primary diagnosis.

The primary feature separating t-MDS (or t-MDS/MPN) from t-AML is the percent blast count, which is <20% in t-MDS (or t-MDS/MPN) and ≥20% in t-AML. Some patients, particularly those treated with topoisomerase II inhibitors, may bypass the MDS phase (Table 20.1).

Table 20.1

Clinicopathologic Features of Therapy-Related AML

Features	Alkylating Agents	Topoisomerase II Inhibitors
Latency period	5–7 years	<5 years
Preceded by MDS	Often present	Often absent
AML subtype	Variable	Mostly monocytic; sometimes promyelocytic or other types
Cytogenetics	Deletions: often del(5) and del(7)	Translocations: t(9;11); t(6;11); t(15;17); t(8;21); t(3;21); t(6;9)
Molecular findings	*AML1/RUNX1* mutations	*AML1/RUNX1* mutations
Clinical outcome	Poor	Favorable

Alkylating Agent/Radiation-Related Myeloid Neoplasms

Alkylating agent / radiation-related AML has a latency period of about 5–7 years and is usually (>70%) preceded by MDS. The average time for progression from MDS to AML is about 5 months. The occurrence rate appears to be dependent on the age of the patient and the total accumulative dose of the chemotherapeutic agents and/or radiation.

The latency period between the diagnosis of the primary disease and the occurrence of t-AML appears to be longer in the younger patients and patients who have been treated with alkylating agents for non-malignant conditions, such as autoimmune disorders. The overall median latency period for the entire t-AML patient population is approximately 65 months with a median survival of about 7 months. Patients with chromosomal deletion of 5 and/or 7 have a shorter median survival time than those with chromosomal translocations.

MORPHOLOGY (FIGURE 20.1)

- The characteristic morphologic features are dysplastic hematopoiesis and increased blasts (including promonocytes). Blasts are <20% in t-MDS and ≥20% in t-AML.
- Dysplastic changes are usually multilineage and involve myeloid, erythroid, and megakaryocytic series. Hypogranulation and abnormal segmentation of the granulocytic cells, megaloblastic changes in the erythroid series, ring sideroblasts, and micromegakaryocytes are frequent findings.
- Most t-AML cases correspond to AML with maturation (AML-M2), but a minority of the cases fit into acute myelomonocytic (AML-M4), acute monocytic (AML-M5), acute erythroleukemia (AML-M6), or acute megakaryocytic leukemia (AML-M7) (See Chapter 21).
- Bone marrow is often hypercellular, but in about 25% of cases is hypocellular. Bone marrow fibrosis may be present in one-fourth of the cases. Basophilia is sometimes present.

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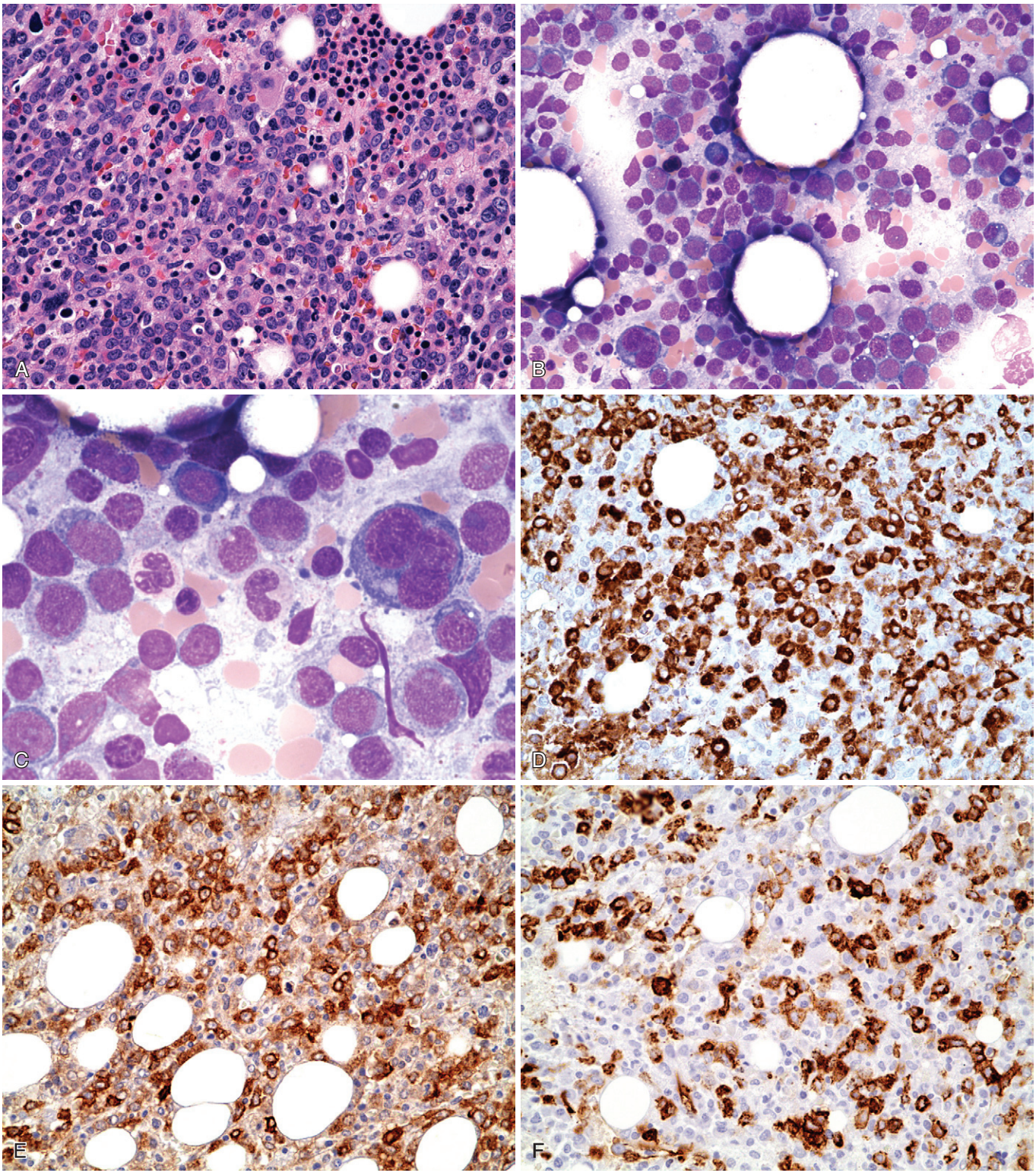

FIGURE 20.1 THERAPY-RELATED AML IN A PATIENT WITH A HISTORY OF HODGKIN LYMPHOMA. Bone marrow biopsy demonstrating hypercellularity with increased blasts (A). Bone marrow smear (B, low power; C, high power) showing dysplastic erythropoiesis and increased blasts. Blasts are positive for MPO (D), CD117 (E) and CD34 (F) by immunohistochemical stains.

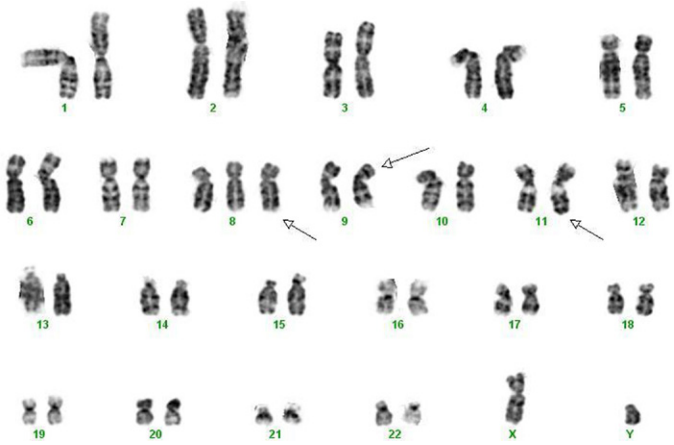

FIGURE 20.2 G-banded karyotype showing t(9;11) and trisomy 8 in a patient with therapy-related AML.

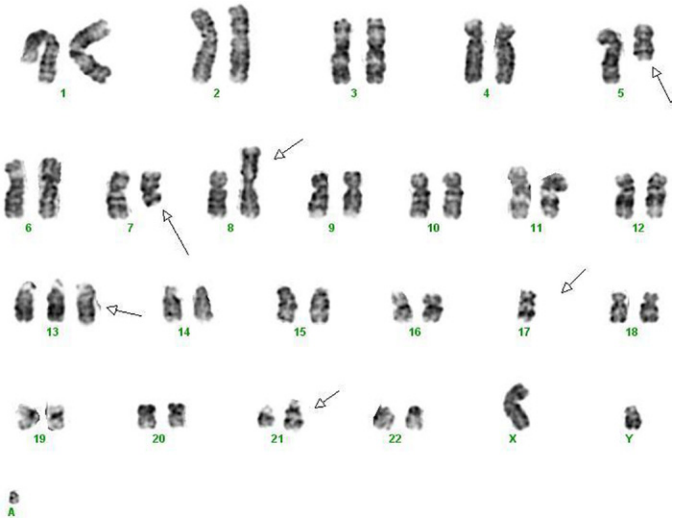

FIGURE 20.3 G-banded karyotype showing a complex karyotype involving chromosomes 5, 7, 8, 13, 17, and 21 in a patient with therapy-related AML.

- The peripheral blood may show anemia or pancytopenia with anisopoikilocytosis and leukoerythroblastic features and presence of blast cells. Dysplastic changes may be noted in the myeloid cells and/or platelets.

IMMUNOPHENOTYPE

Flow cytometry is important in enumerating and determining phenotypic patterns of the blasts, as well as detecting dysmaturation patterns of myelomonocytic cells. The immunophenotypic pattern of the blasts in t-AML is similar to that seen in various subtypes of AML, NOS (Chapter 21).

MOLECULAR AND CYTOGENETIC STUDIES

- Over 90% of alkylating agent / radiation-related AMLs show clonal chromosomal aberrations, most frequently involving loss of all or part of chromosome 5, chromosome 7, or both.
- Balanced chromosomal translocations are rare and mostly involve 11q23 or 21q22 (Figure 20.2). Some reports show an association between radiation t-AML and t(15;17) or inv(16). The karyotypes are often complex (Figure 20.3) with nonclonal or single cell aberrations and not consistently observed in consecutive follow-up studies.
- These treatment-related aberrations are frequently seen in addition to those seen in primary myeloid malignancies.
- Radiotherapy-related AML cases have been associated with acquired *AML1/RUNX1* mutations.

Topoisomerase II Inhibitor-Related AML

Topoisomerase II inhibitor-related AML generally has a shorter latency period than the alkylating agent-related neoplasms, ranging from 1 to 3 years. An antecedent myelodysplastic phase is usually lacking. Anthracyclines, doxorubicin, etoposide, epipodophyllotoxins, and teniposide are among the major drugs targeting DNA topoisomerase II. The median survival time is longer for topoisomerase II inhibitor-related AML than for alkylating agent-related AML. Balanced translocations are frequent cytogenetic abnormalities.

MORPHOLOGY (FIGURE 20.4)

- Myelodysplastic features are infrequent and in most instances the disease presents itself as a *de novo* AML.
- The most common morphologic features are those of acute myelomonocytic or acute monocytic leukemias (see Chapter 21), but some cases may present morphologic and cytogenetic features consistent with acute promyelocytic leukemia (APL).

IMMUNOPHENOTYPE

See immunophenotypic features of APL, acute myelomonocytic leukemia, and acute monocytic leukemia (Chapters 18 and 21).

MOLECULAR AND CYTOGENETIC STUDIES

- Topoisomerase II inhibitor-related AML is commonly associated with complex chromosomal aberrations and translocations, particularly involving *11q23* and the *MLL* gene (Figures 20.5 and 20.6). The 11q23-associated cytogenetic changes include del(11q23), (6;11)(q26–27;q23), t(9;11)(p22;q23), (10;11)(p12;q23), and t(11;19)(q23;p13.1).

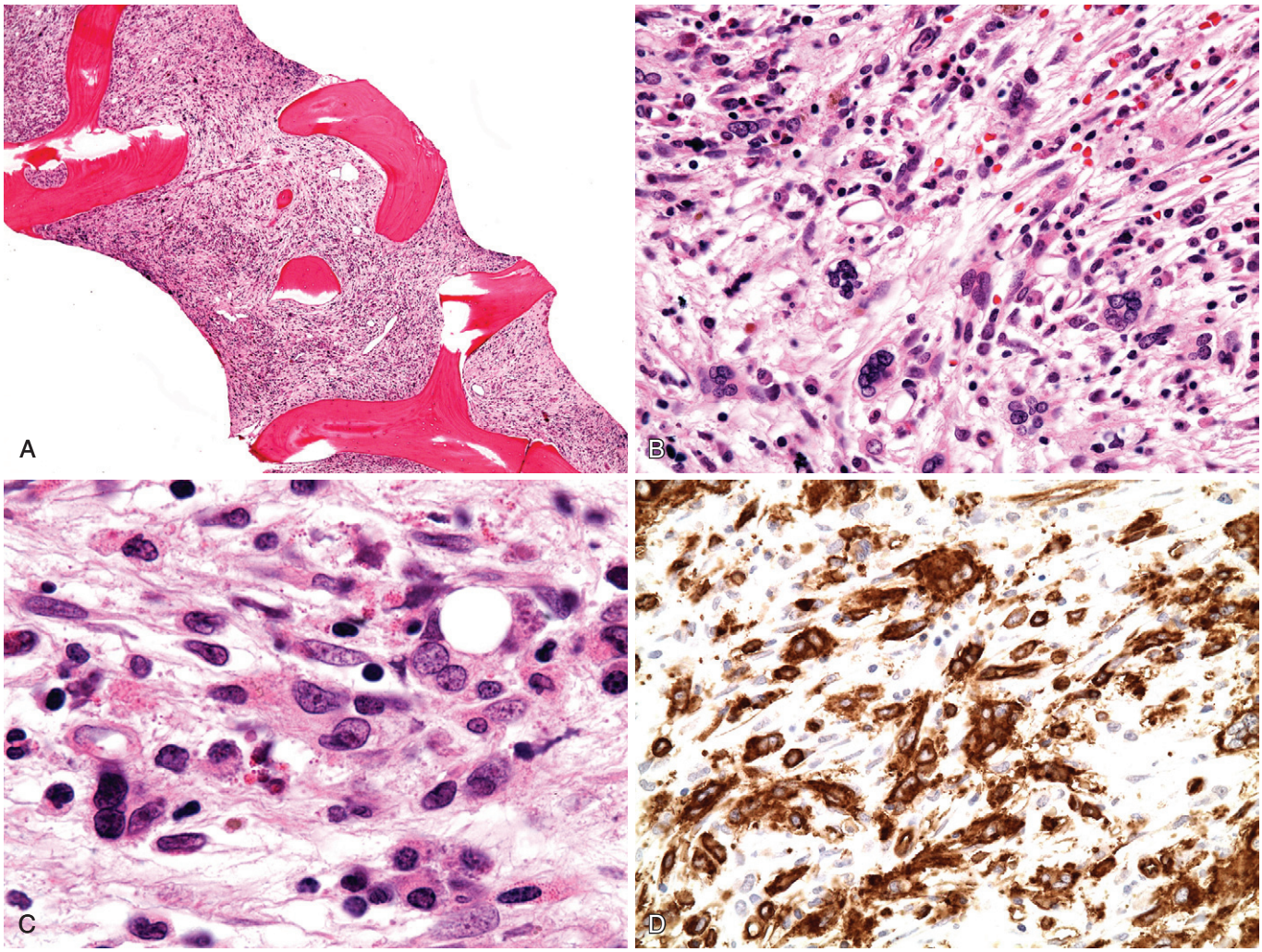

FIGURE 20.4 THERAPY-RELATED AML IN A 20-YEAR-OLD MALE WHO HAD A HISTORY OF ANAPLASTIC LARGE CELL LYMPHOMA STATUS CHEMOTHERAPY 3 YEARS PREVIOUSLY. Marrow core biopsy section shows extensive fibrosis (A) with excess blasts in small abnormal clusters (B). Many of the blasts are spindle-shaped, containing smooth to slightly irregular nuclei, dispersed chromatin, and prominent nucleoli (C). Immunohistochemical stain for CD34 highlights numerous blasts (D).

- Other cytogenetic abnormalities such as t(15;17)(q22;q11–12), (3;21)(q26;q22), t(8;21)(q22;q22), t(6;9)(p23;q34), and t(8;16)(p11;p13) have also been reported in topoisomerase II inhibitor-related AMLs.
- Occasionally, the chromosomes exhibit homogeneous staining regions (hsr) or double minutes (dm) at various genomic sites and represent amplifications of the MLL locus (Figures 20.7 and 20.8).
- As in radiation-associated AML, *RUNX1* gene mutations have been found in topoisomerase-associated AML cases.

Differential Diagnosis

The differential diagnosis of the therapy-related myeloid neoplasms includes various morphologic categories of AML (see Chapter 21) as well as AML with myelodysplasia-related changes. The most distinguished feature is a history of cytotoxic or radiation therapy.

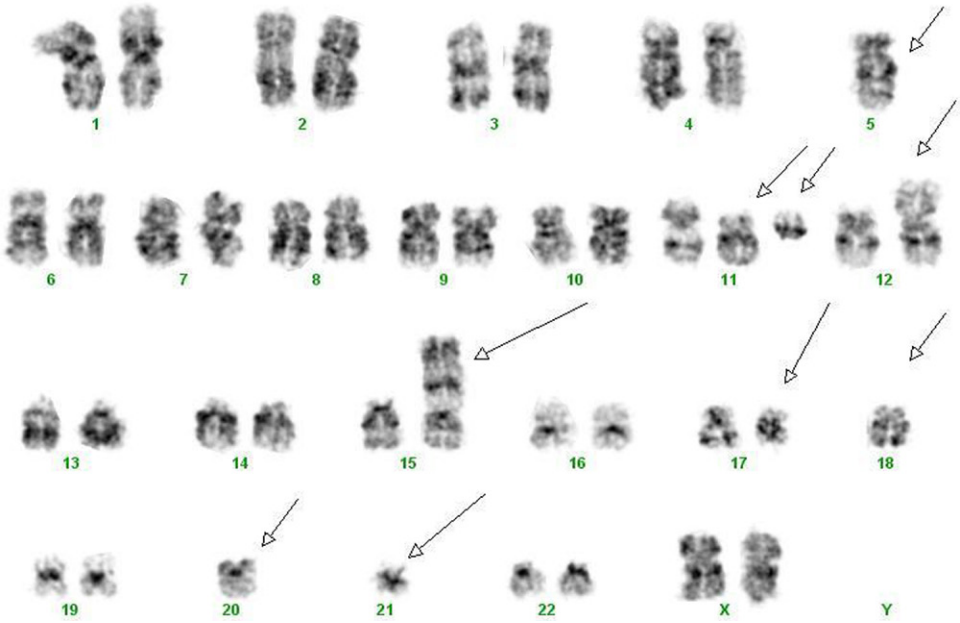

FIGURE 20.5 G-banded karyotype demonstrating complex chromosomal aberrations involving chromosomes 5, 11, 12, 15, 17, 18, and 20, and 21 in a patient with therapy-related AML.

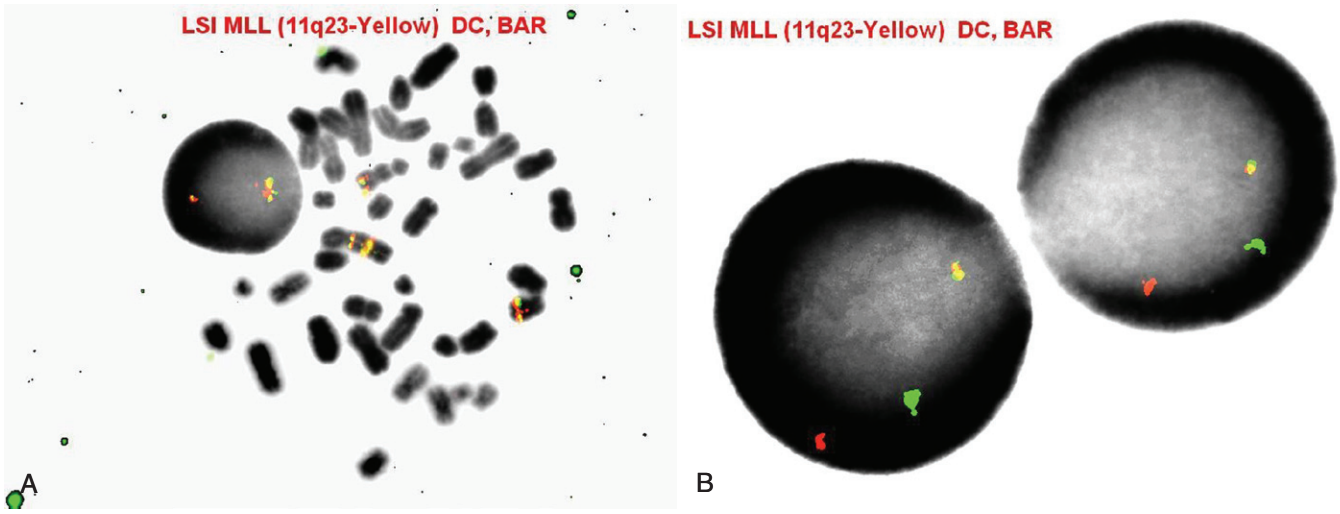

FIGURE 20.6 FISH analysis (A and B, yellow dots) showing *MLL* rearrangement in a patient with therapy-related AML.

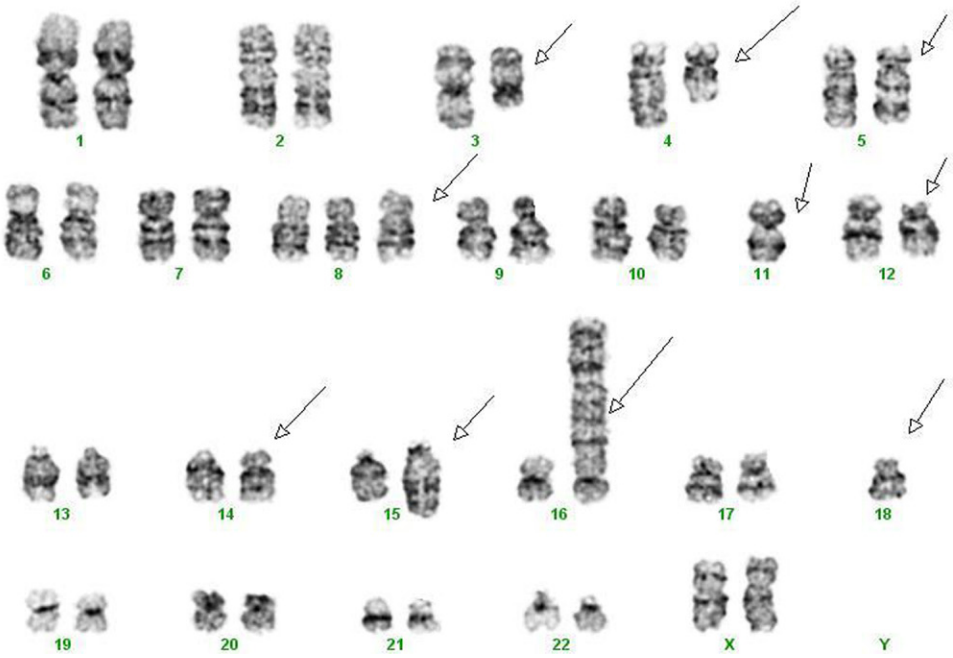

FIGURE 20.7 G-banded karyotype showing complex chromosomal aberrations with homogeneous staining regions (hsr) at 16p in a patient with therapy-related AML.

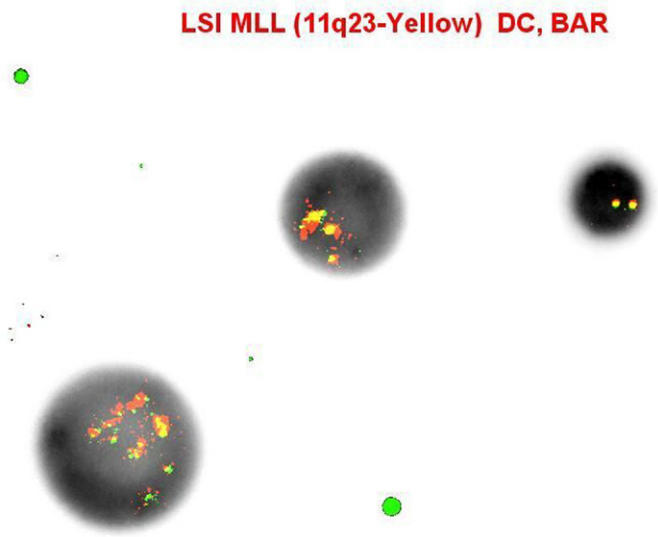

FIGURE 20.8 FISH analysis demonstrating amplification of the *MLL* locus in a patient with therapy-related AML.

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