Chapter 7 Acute leukemia

There are two main types of acute leukemia: myeloid (AML) and lymphoblastic (ALL). Acute leukemias are blastic proliferations of white cells that usually but not invariably involve the peripheral blood. The exact definition of particular subtypes is often arbitrary (defined by committee consensus) and much unnecessary confusion between histologist and hematologist/oncologist can be avoided by comparing specimens and relating findings to individual patients. This is especially the case when dealing with the overlap between lymphoma and leukemia.

Both acute leukemias affect all ages although their frequencies are quite different. AML is primarily an adult disease with the incidence rising with age whereas more than 85% of cases of ALL are in children aged under 15 years. The prognosis in ALL in children is excellent whereas in AML it is generally poor, particularly in the elderly. Some studies give those over 55 years only a 2% chance of 5-year survival regardless of therapy.

Classification

Since the first edition of this text there has been a major change in the classification of acute myeloid leukemia. The French–American–British (FAB) group classification which had achieved wide acceptance for both AML and ALL[1,2] was based solely on cytologic appearances. It has become increasingly recognized that this is not adequate for clinical purposes and that the underlying cytogenetic abnormalities must also be considered. The clinical importance of these changes cannot be overemphasized and they have been incorporated into the WHO classification published in 2001 where full details can be obtained by the interested reader. AML is now divided into four major groups:

1 AML with recurrent genetic abnormalities: t(8;21), inv(16), 11q23 and t(15;17)
2 AML with multilineage dysplasia
3 AML, therapy related
4 AML not otherwise categorized

Acute myeloid leukemia

Classification

From the point of view of the pathologist these changes have very little effect. Indeed the chapter in the WHO book makes only passing references to histology in all of these categories. Basically, in the first three categories the histology is remarkably similar as we commented previously for the FAB classification. If one is lucky, histology might recognize the t(15;17) promyelocytic leukemias and significant associated dysplastic changes can help recognize category 2. Otherwise the best we can do is identify lineage differentiation in category 4 as monocytic, erythroid or megakaryocytic, just as we did previously for the FAB classification.

Histopathology and immunophenotyping

Acute myeloid leukemia

Another important difference between the WHO classification and the FAB system is that the blast cell count necessary for a diagnosis of AML is reduced from 30% to 20%. The essential contribution of the pathologist is to recognize the blasts as myeloid not lymphoid and to give an estimate of their percentage and distribution. There is no definitive immunophenotype for AML as it is an extremely heterogeneous condition but most cases in WHO categories 1–3 will be myeloperoxidase positive and negative for B and T cell markers. There are some exceptions to this as CD2, CD7 and CD9 can be detected in some cases but provided they are myeloperoxidase positive a diagnosis of AML should be made. Exceptions to this rule are those rare primitive AMLs previously labeled M0 which lack most antigens although with luck will be terminal deoxynucleotidyl transferase (TdT) positive (Fig. 7.1). Other helpful markers are TdT (more commonly positive on ALL though), c-kit (CD117), CD34 and CD56 (Fig. 7.2).

Acute promyelocytic leukemia is difficult to detect histologically

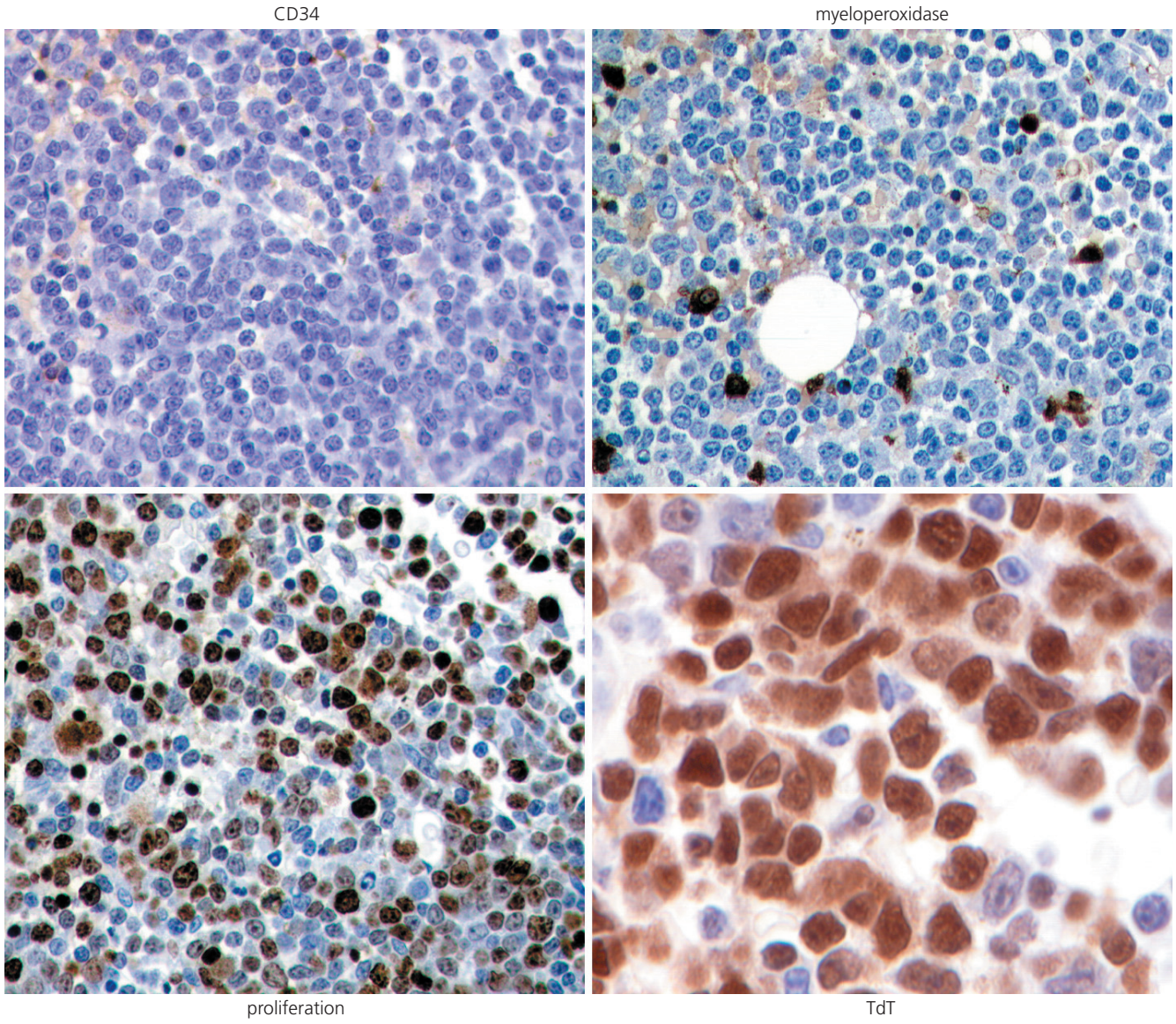
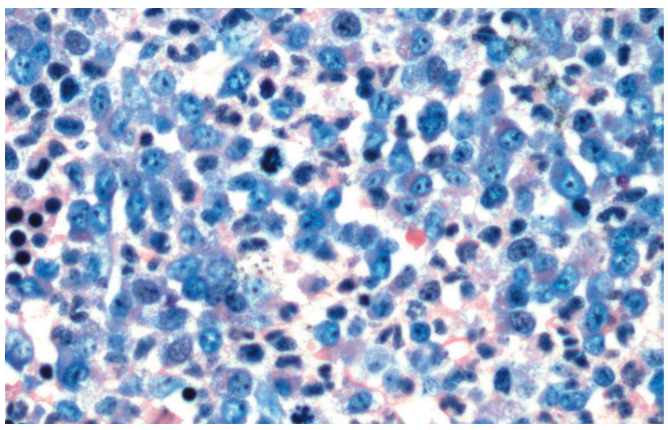
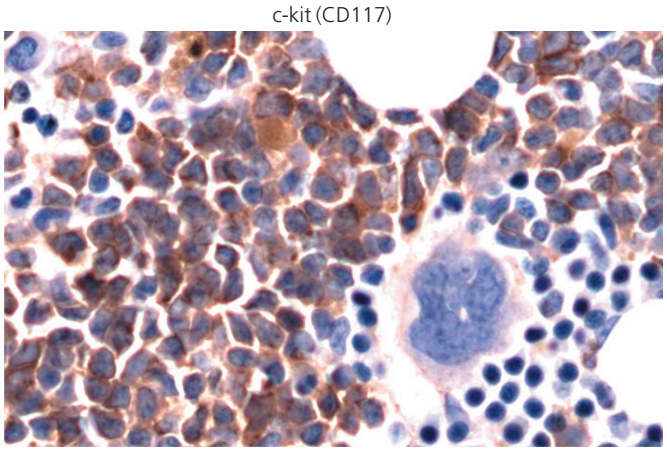


Fig. 7.1 Primitive case of acute myeloid leukemia (AML) positive only for terminal deoxynucleotidyl transferase (TdT).

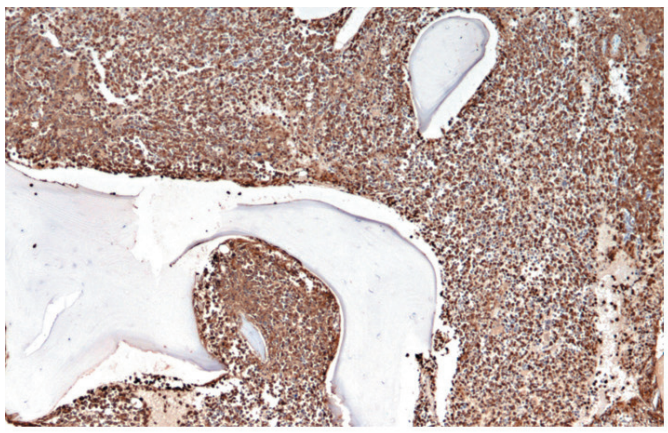
Giemsa



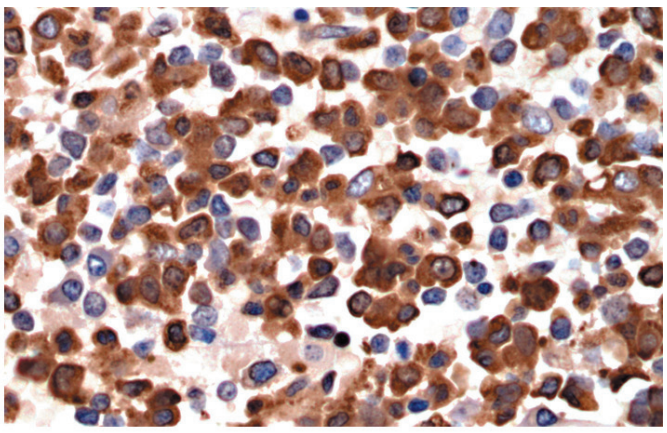
c-kit (CD117)



myeloperoxidase

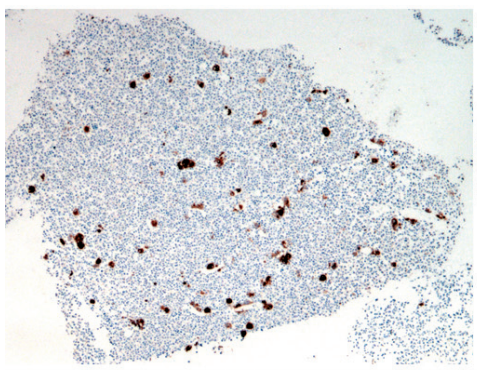


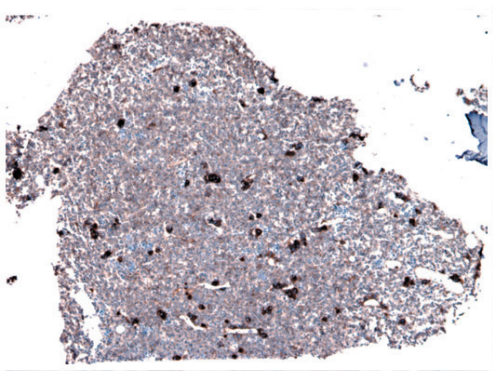
CD61

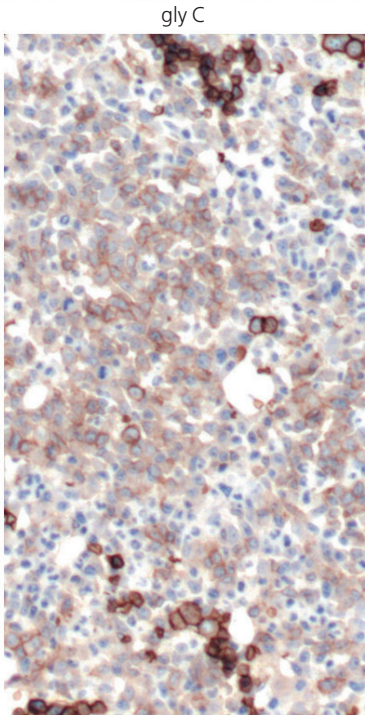


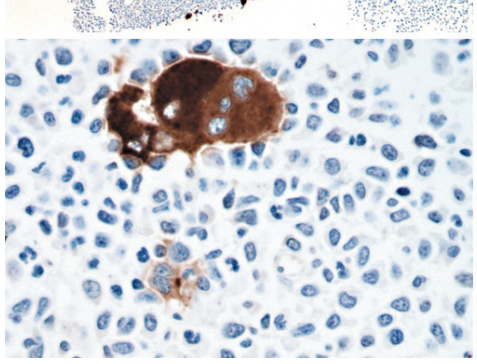
CD31

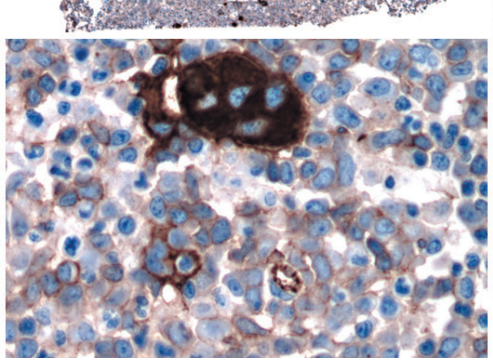
gly C











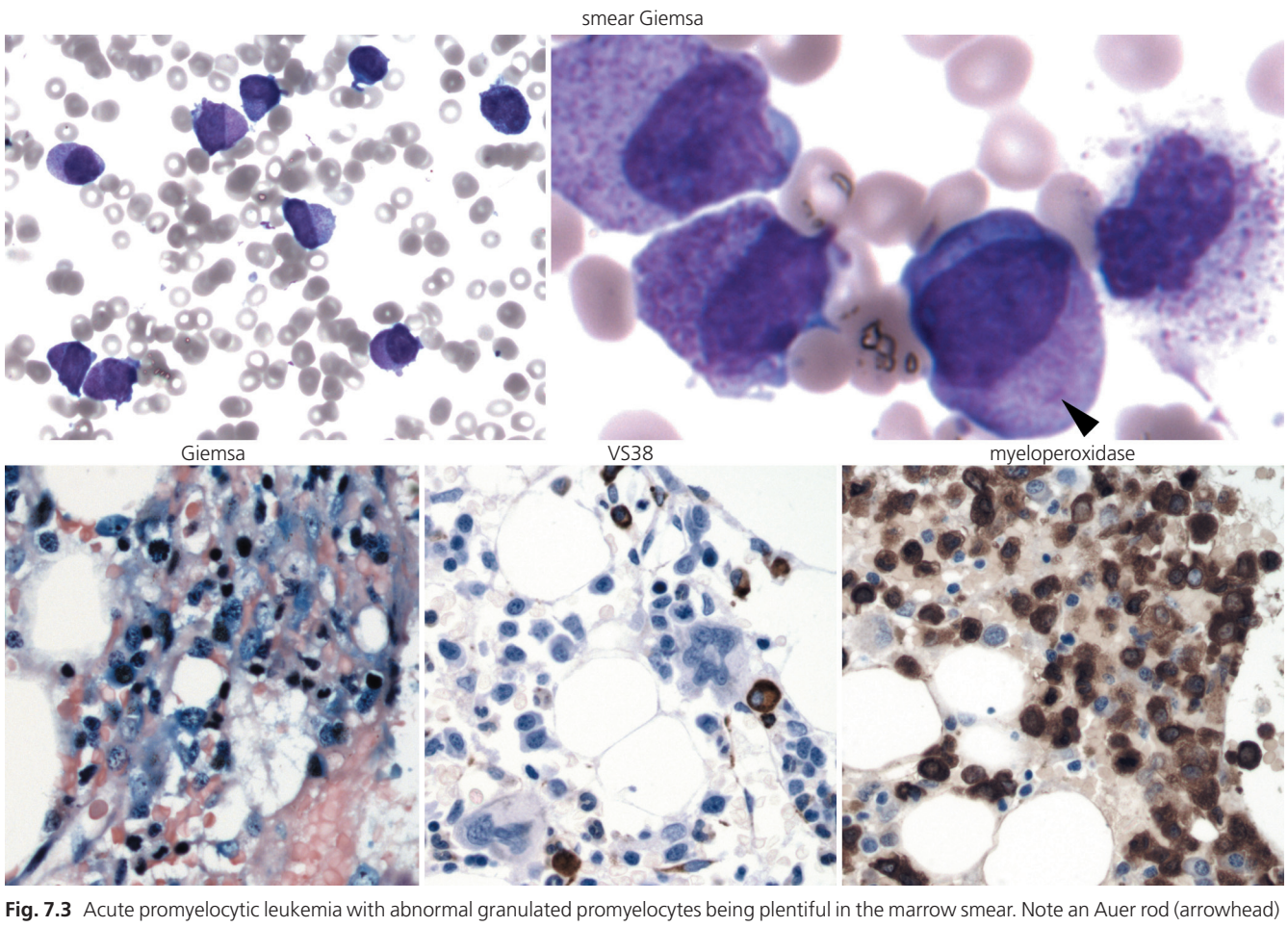


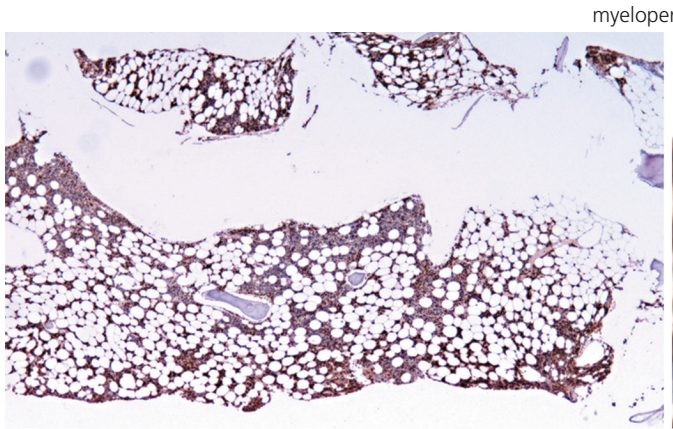
Fig. 7.3 Acute promyelocytic leukemia with abnormal granulated promyelocytes being plentiful in the marrow smear. Note an Auer rod (arrowhead) in the high power. The histology can be confusing at times. This case has a lymphoplasmacytic appearance but is negative for plasma cell markers (VS38) and other lymphoid antigens but positive for myeloperoxidase.

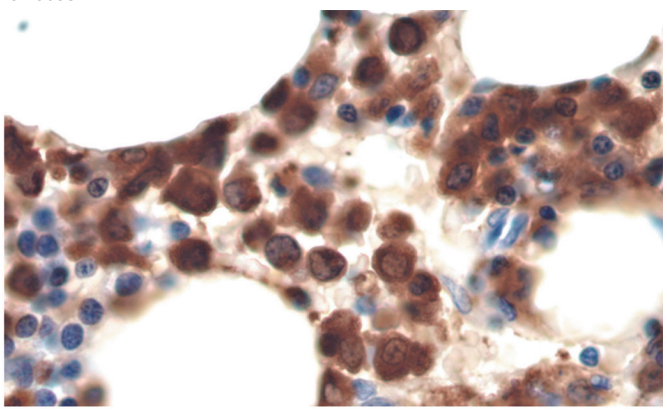
and careful liaison with the hematologists or inspection of the smears in needed (Fig. 7.3). Antibodies recognizing the PML gene product patterns, which would be very helpful, are still not available for use on paraffin sections.

Occasionally AML is sufficiently patchily distributed throughout the marrow that a confident diagnosis cannot be made on cytology alone and here histology provides essential information for the clinician (Fig. 7.4). Category 2 AML (i.e. that arising with or from myelodysplasia) is important to recognize as it has a poor prognosis. While this information is usually known by the clinicians, histology can highlight this quite successfully in many cases (Fig. 7.5). Finally, there will always be odd cases that have unusual immunophenotypes which require careful clinical correlation so as not to misdiagnose AML as lymphoma or vice versa (Fig. 7.6).

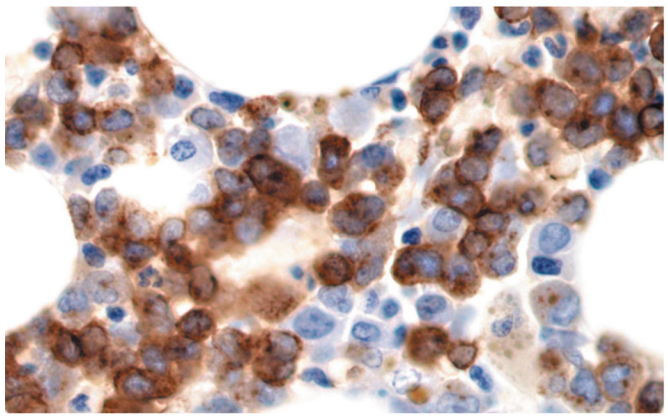
Fig. 7.2 (opposite) Typical case of AML positive for myeloperoxidase and c-kit (CD117). Note for interest the weak positivity for CD31 which is not lineage specific and glycophorin C; such so-called anomalous findings are common in AML.

myeloperoxidase

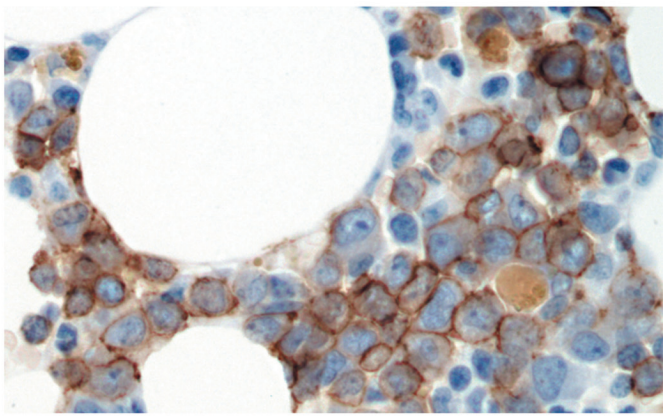




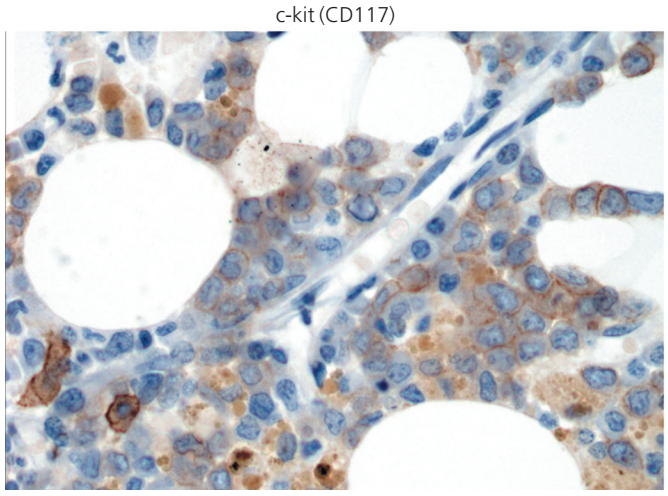
CD34



CD56



c-kit (CD117)



Giemsa

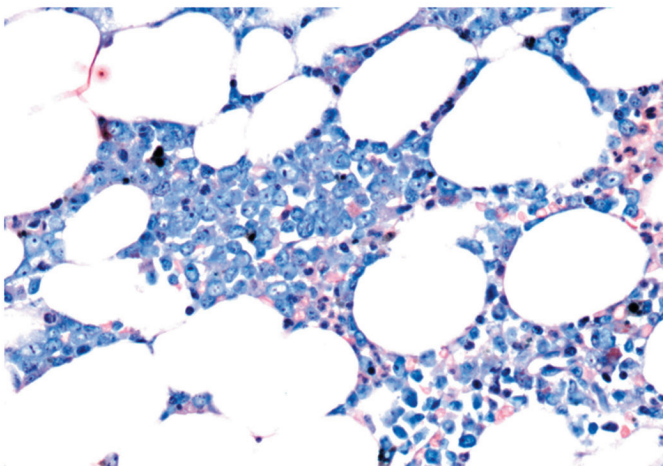


Fig. 7.4 Case of AML with a patchy distribution in the marrow which was inconclusive on aspirate examination. The biopsy is diagnostic showing large numbers of blasts immunostaining for myeloperoxidase, CD34, CD56 and c-kit (CD117).

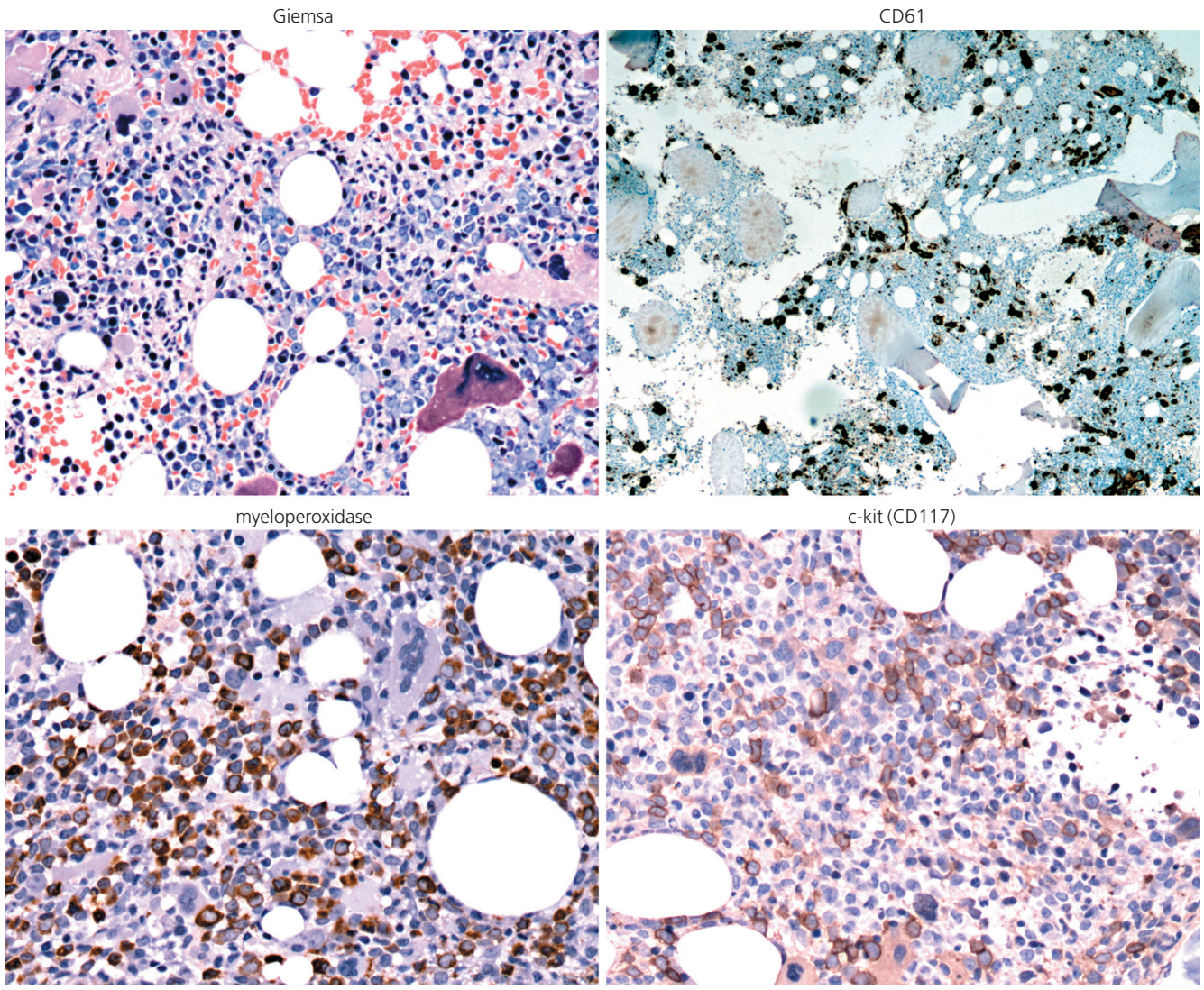


Fig. 7.5 AML arising from a dysplastic marrow (well demonstrated by the megakaryoctic pattern with CD61). Myeloperoxidase and c-kit (CD117) immunostains outline the substantial blast cell population.

Therapy related AMLs can be extremely difficult to diagnose as they are often mixed up with dysplastic marrow elements which represent regenerative changes as much as true myelodysplasia. Careful immunophenotyping and, if possible, comparison with the underlying condition that was treated will usually sort out the true diagnosis (Fig. 7.7). Of course it should never be forgotten that at the same time as a secondary AML arises the previous condition itself may also relapse (Fig. 7.8).

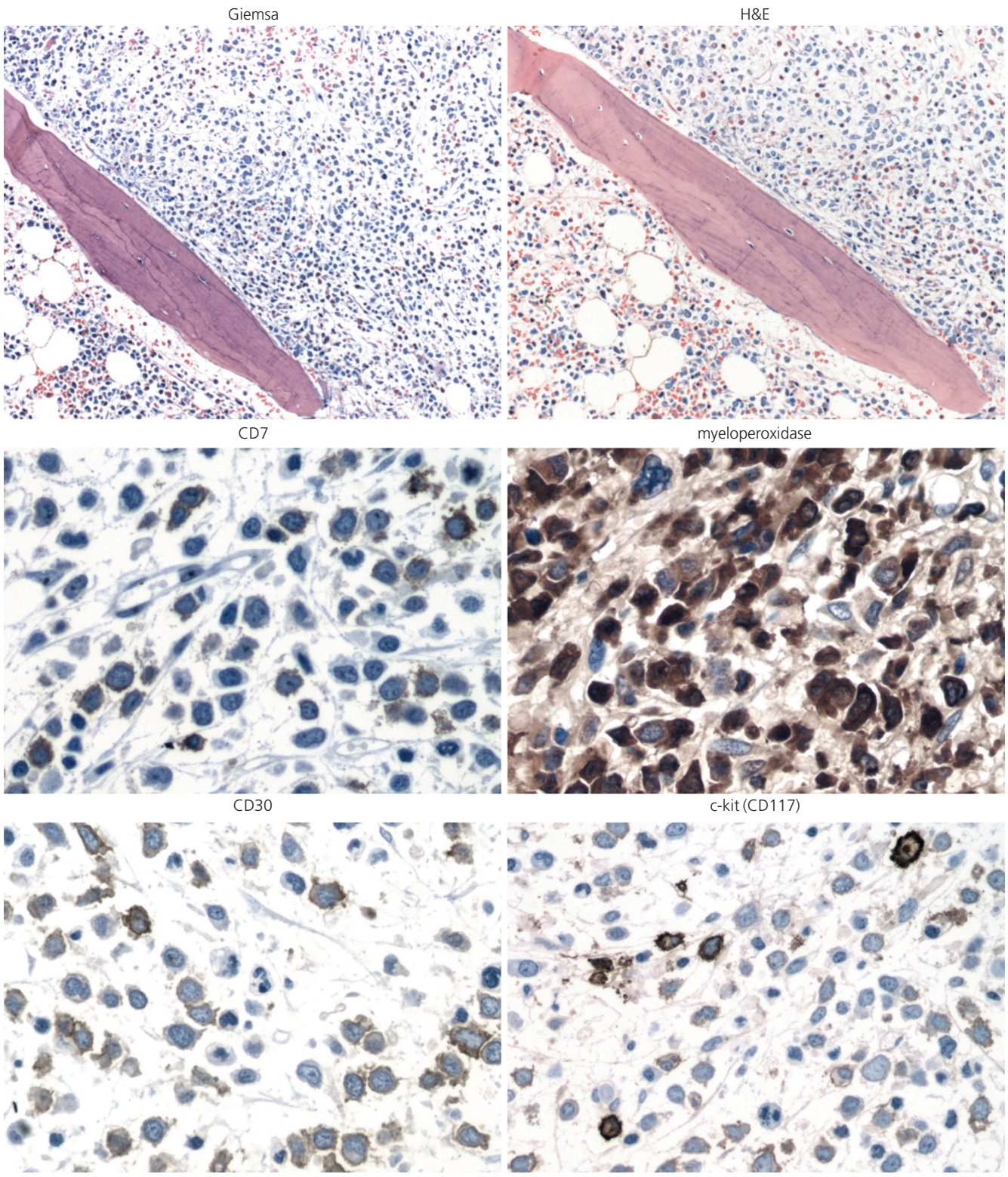
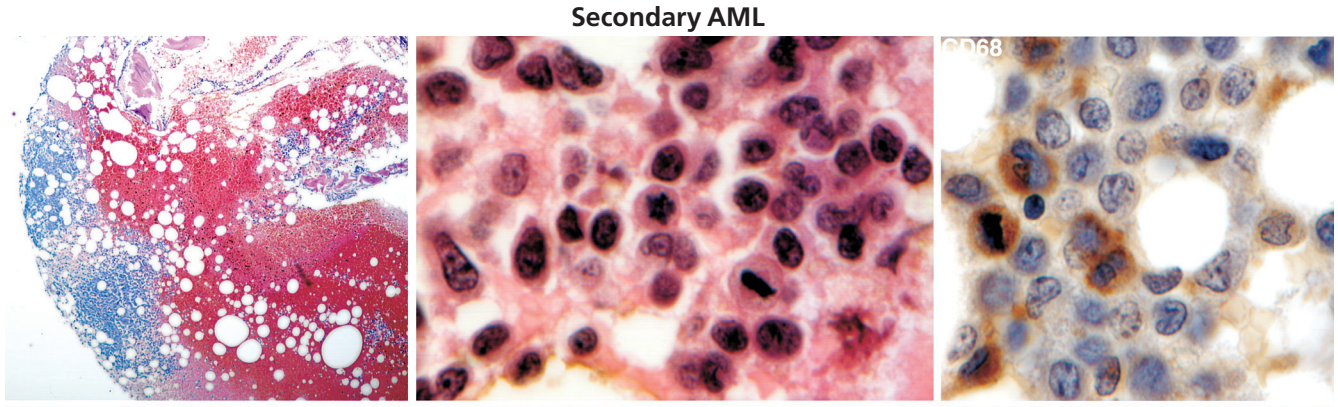
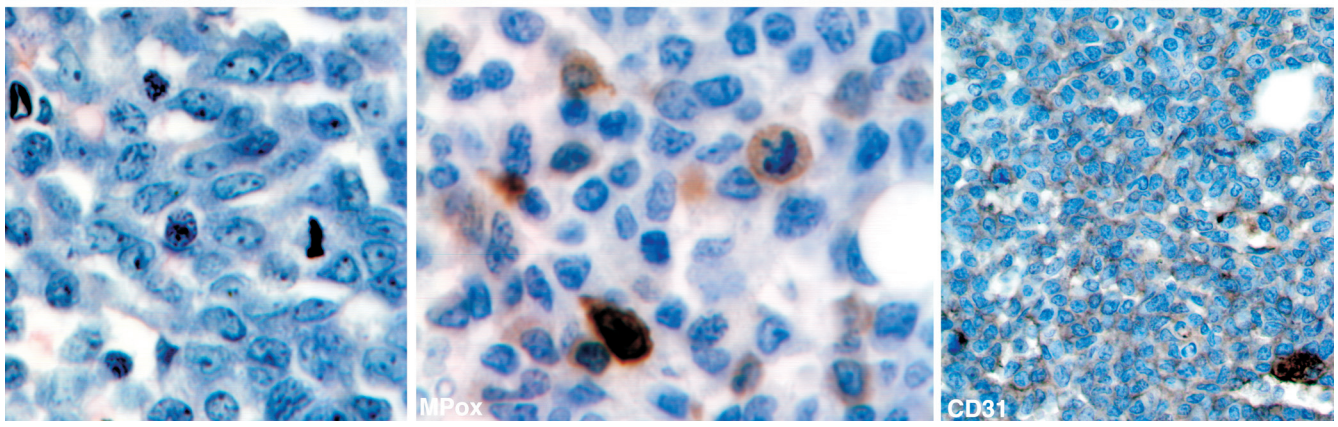


Fig. 7.6 An unusual case of AML that was positive for CD30 and CD7, raising the question whether it was lymphoid in origin. Myeloperoxidase and to a lesser extent c-kit (CD117) positivity on the blasts reveals its true nature.

Secondary AML





Original ALL

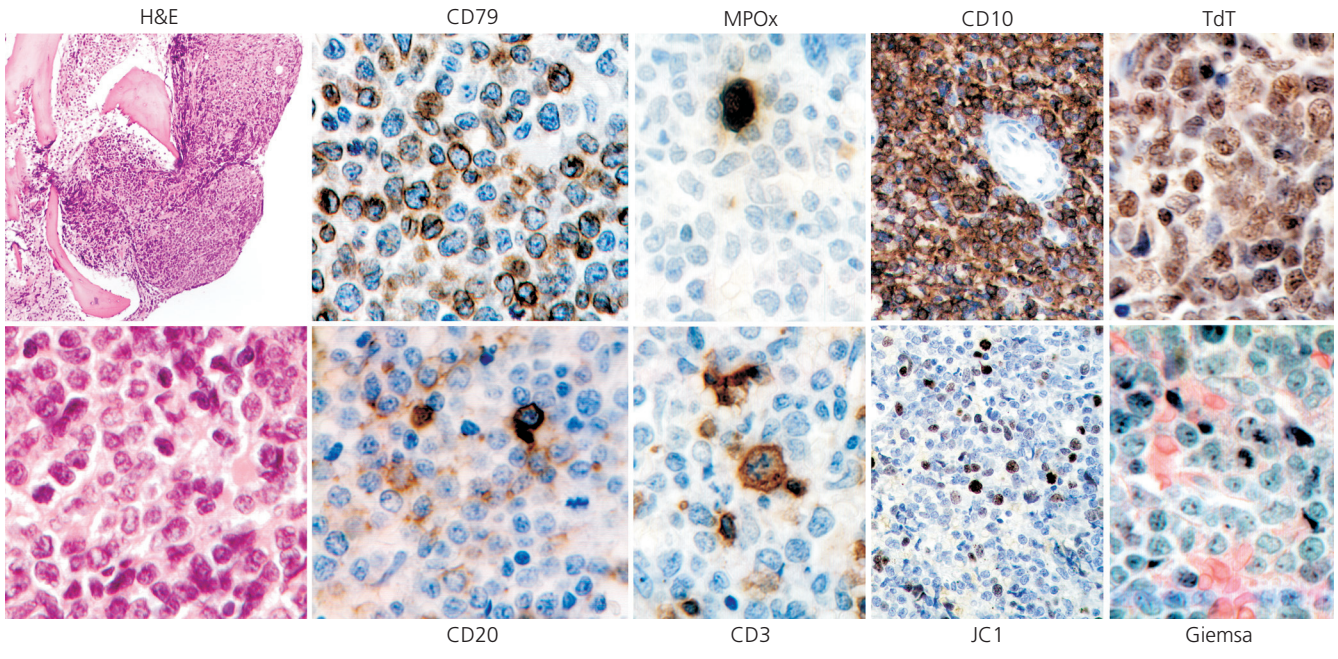


Fig. 7.7 Secondary AML positive only for CD68 suggesting a monoblastic lineage. This case arose 2 years after therapy for ALL which is shown at the bottom of the figure and has an entirely different immunophenotpye.

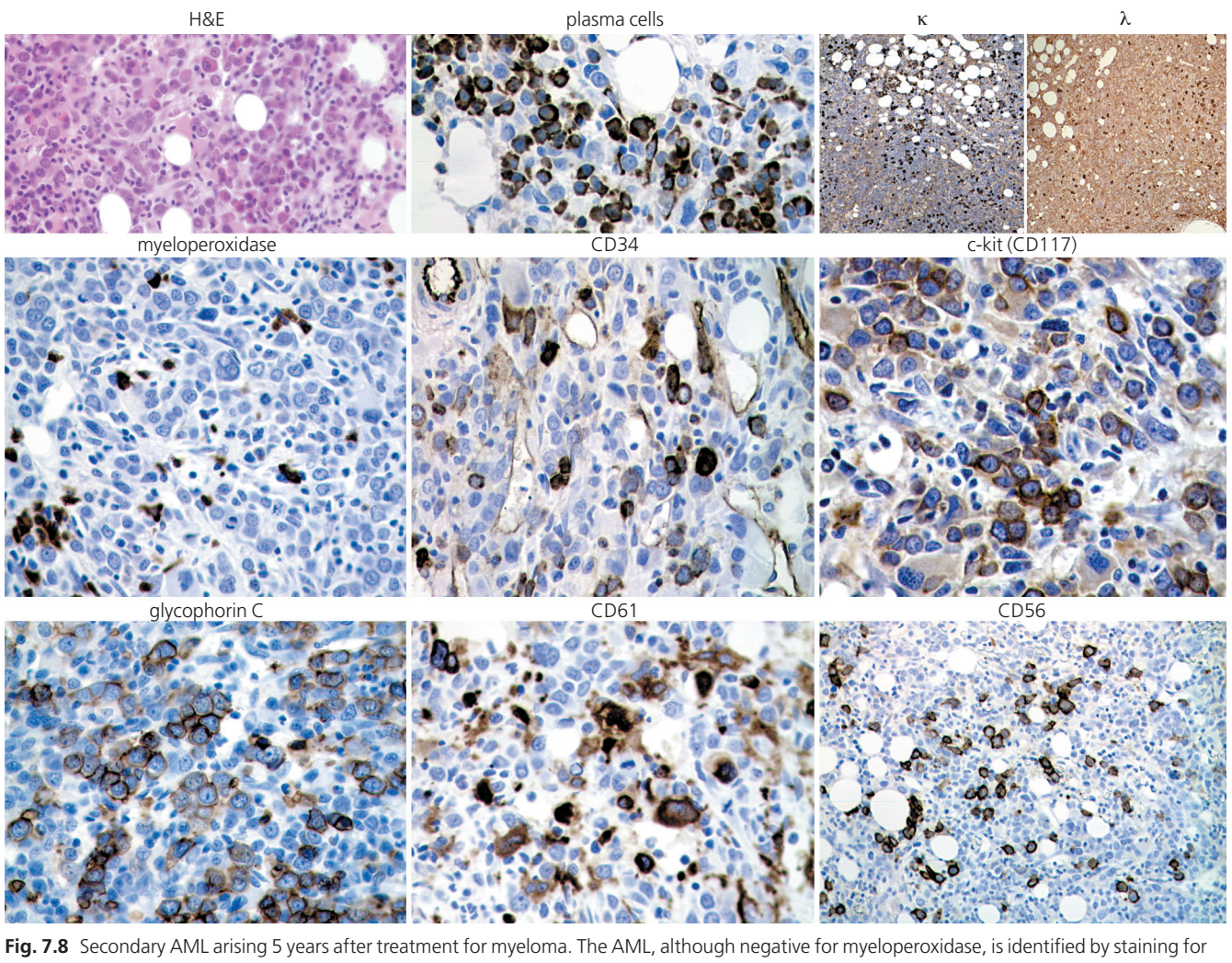


Fig. 7.8 Secondary AML arising 5 years after treatment for myeloma. The AML, although negative for myeloperoxidase, is identified by staining for c-kit (CD117), CD56, CD34, glycophorin C and CD61. As well as this complex AML there is also present a relapse of the myeloma demonstrated by staining for VS38 and light chains (κ and λ).

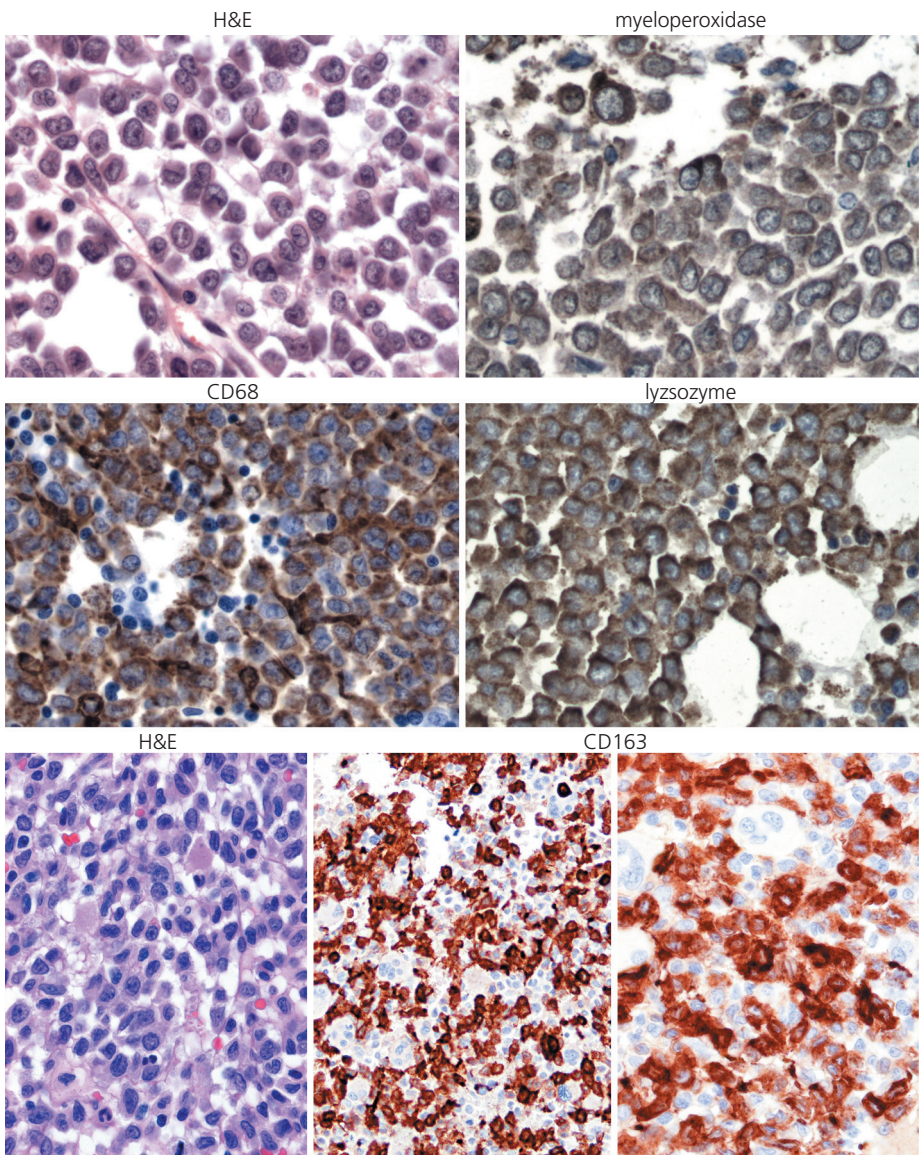


Fig. 7.9 The first four images are of an acute monoblastic leukemia identified by positivity for CD68 and lysozyme. Most cases are negative for myeloperoxidase although this one shows that exceptions occur. The second case (bottom three images) illustrates the value of CD163 in highlighting infiltration by monoblastic leukemia.

Myelomonocytic and monoblastic leukemias

These are important AML subtypes to recognize as they frequently lack myeloperoxidase. In these cases monocytic markers, especially CD68, CD163 and lysozyme, are very important in reaching the diagnosis. Monoblastic leukemia in particular can be confusing as it often presents with extramedullary masses, causing suspicions of lymphoma to be raised (Fig. 7.9).

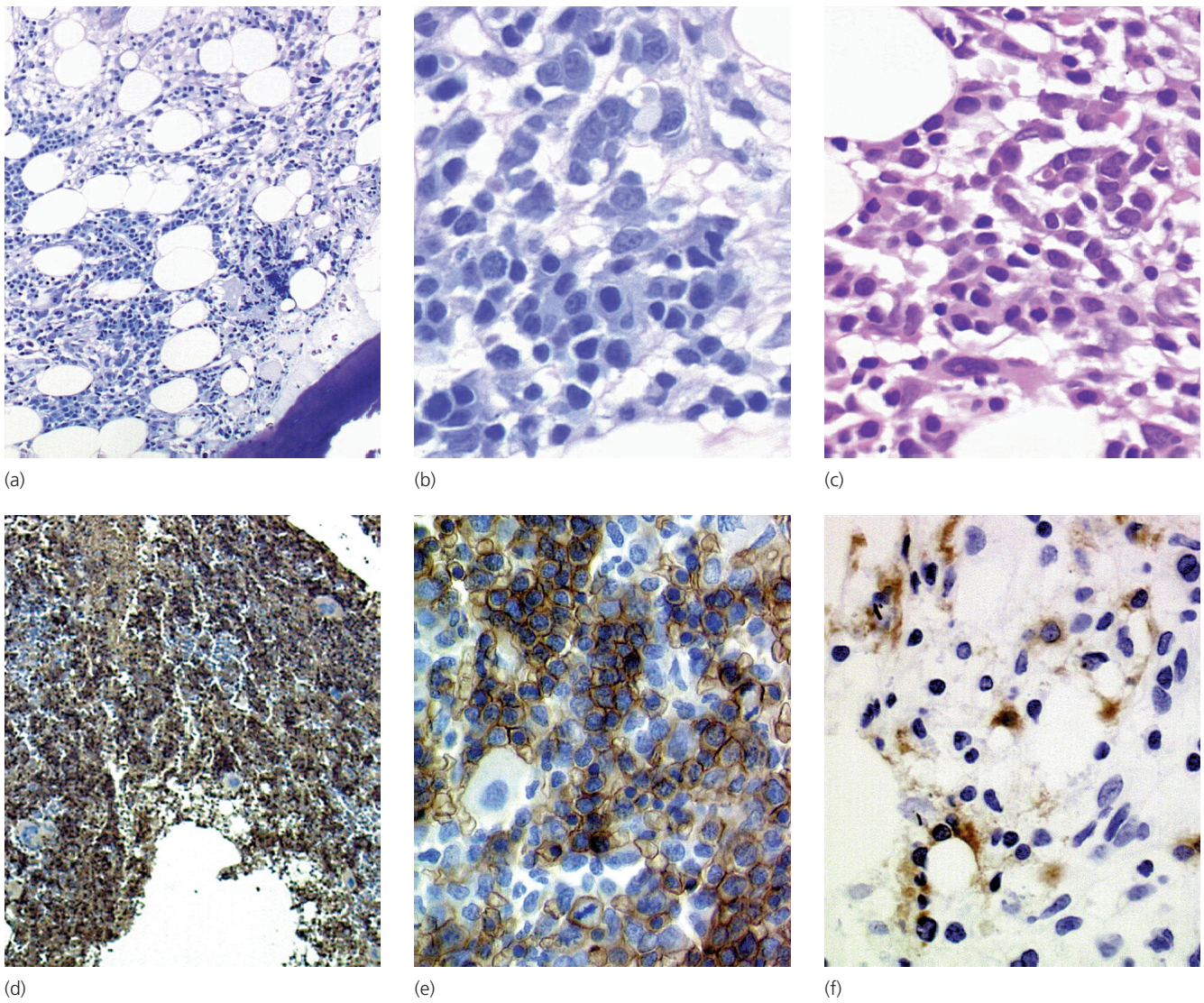


Fig. 7.10 M6 erythroleukemia. The histology is shown in (a,b) Giemsa and (c) H&E. The majority of the cells are erythroid as shown by glycophorin C staining (d,e) but many abnormal cells express other lineage markers such as the megakaryocytic antigen CD61 (f).

Erythroleukemia M6

This is a rare category which it is easy to overlook as myelodysplasia with excess blasts, indeed the borderline between these two conditions is quite uncertain. The erythroid element is predominantly associated with dysplastic erythroid colonies whereas the lineage of most of the true leukemic blasts is uncertain (Fig. 7.10). In cases of doubtful lineage it is probably better to categorize them as AML rather than force a diagnosis of erythroleukemia.

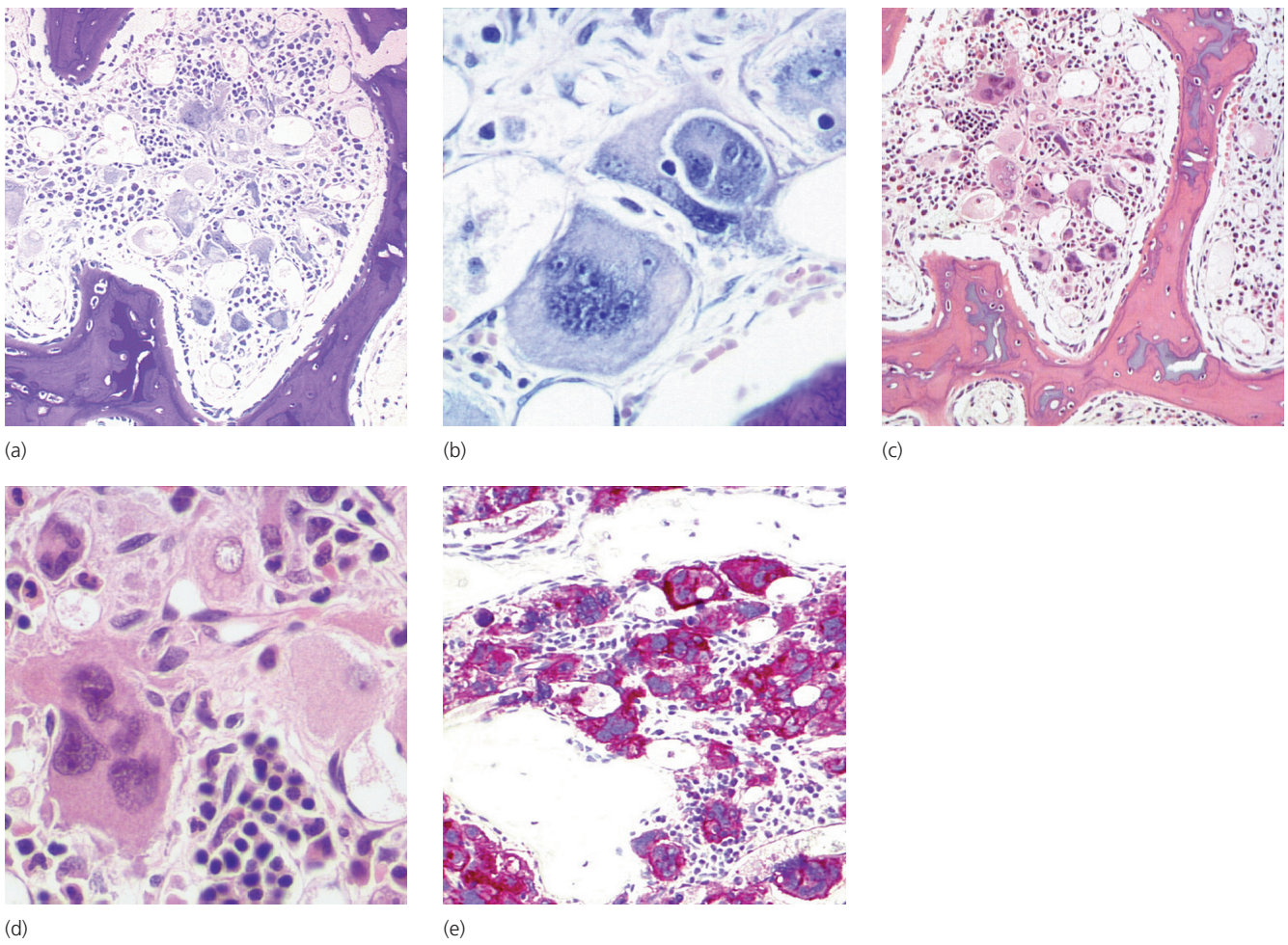


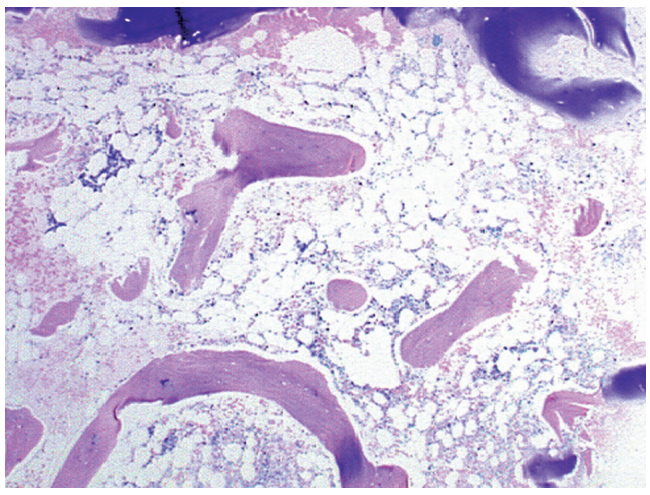
Fig. 7.11 Example of an obviously megakaryocytic leukemia. (a,b) Giemsa. (c,d) H&E. (e) CD31 immunostain.

Megakaryoblastic and megakaryocytic leukemia M7

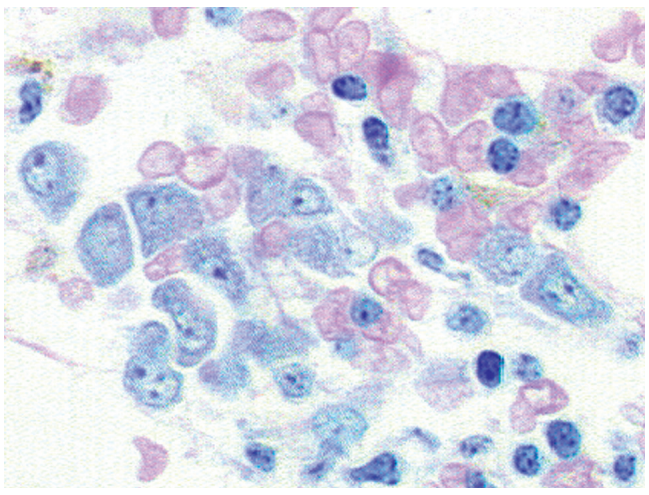
This acute leukemia has a variable morphology from the recognizably megakaryocytic to the frankly bizarre where it can be identified only on the basis of immunocytochemistry. As mentioned in Chapter 6 on myeloproliferative diseases, many cases of acute myelofibrosis are examples of M7 leukemia (Fig. 7.11).

Hypoplastic AML

These patients present with pancytopenia and a "dry tap" on aspiration. Aplastic anemia is usually the main differential, although leukemia is often suspected clinically due to a few suspicious blast-like cells being seen in the peripheral blood. The trephine usually makes the diagnosis by showing discrete collections of primitive blast cells in an otherwise empty marrow. It is said that hypocellular AML should be distinguished from hypocellular myelodysplastic syndrome (MDS). It is common to find evidence of both conditions so that distinguishing hypocellular AML from refractory anemia with excess blasts is not always easy. AML should not be diagnosed unless more than 20% of the cells can be clearly identified as blast cells (Fig. 7.12).



(a)



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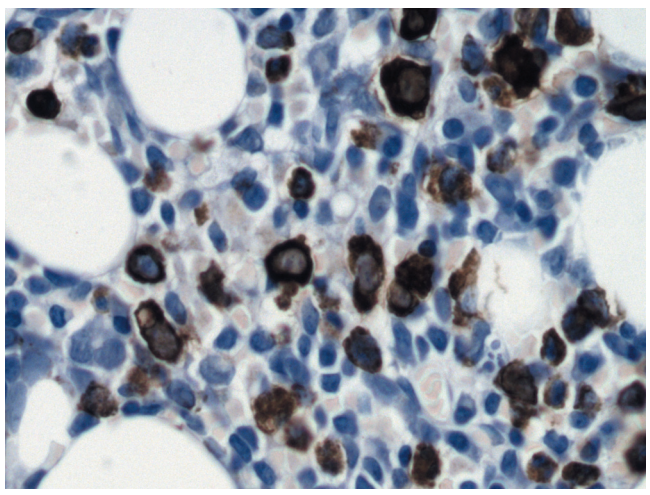

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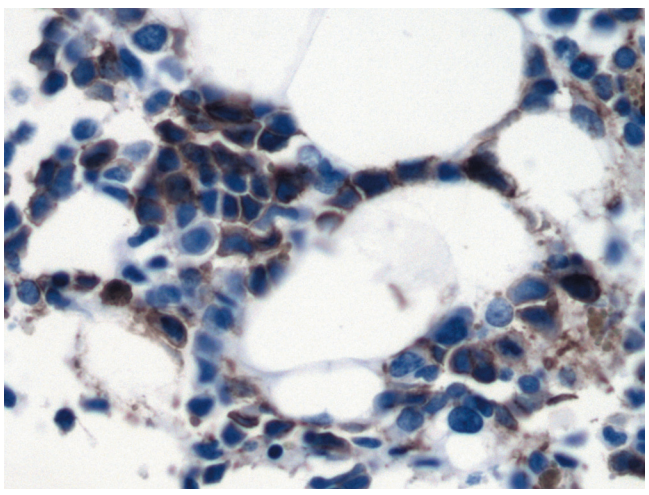
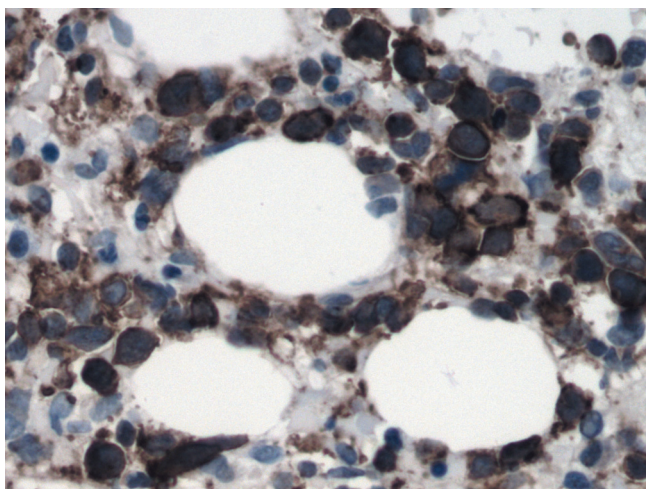


(d)



(e)

Fig. 7.12 An example of a hypocellular marrow (a) in which the majority of cells present are clearly blasts, (b) Giemsa, (c) myeloperoxidase, (d) CD34 and (d) c-kit (CD117).

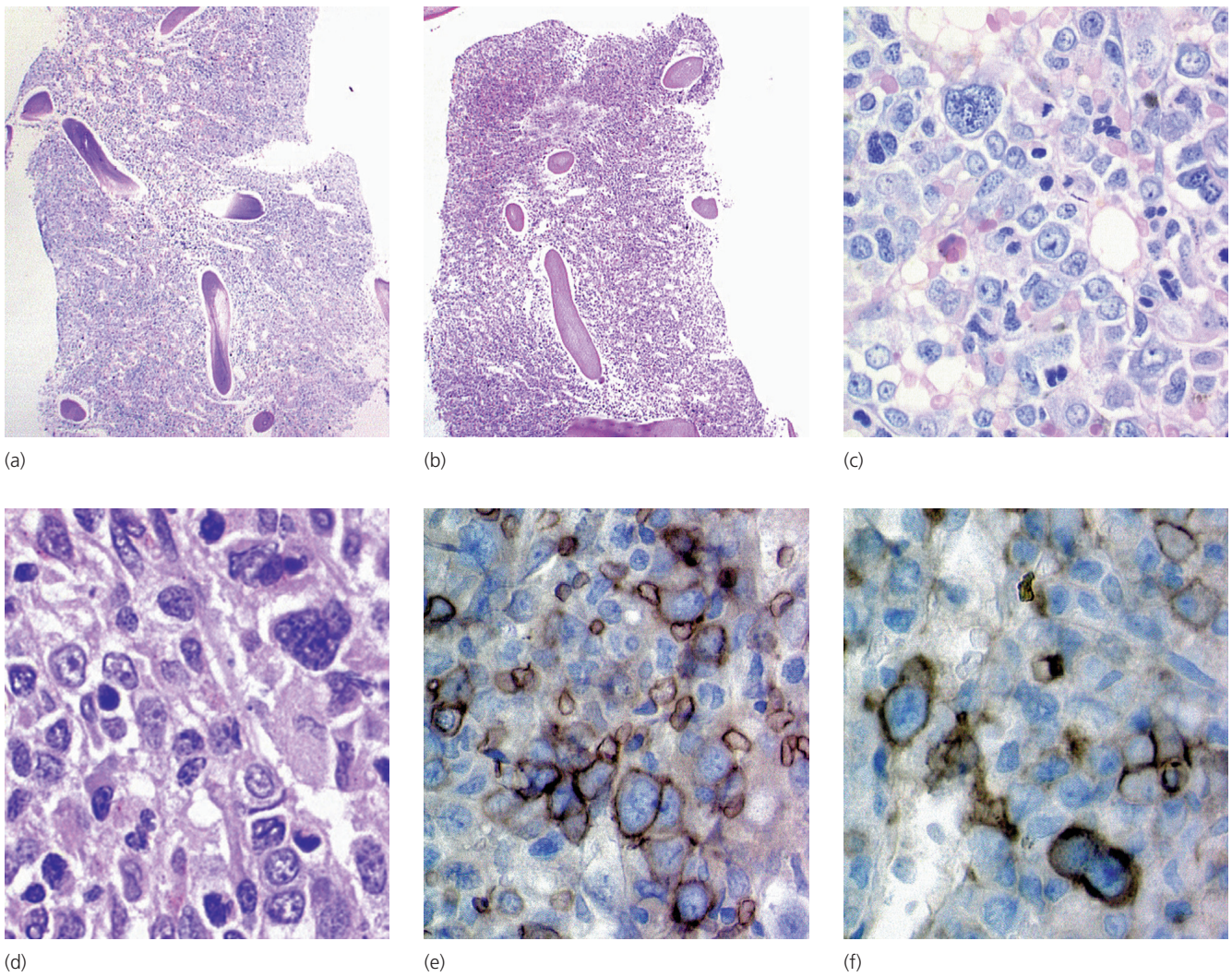


Fig. 7.13 Hypercellular marrow (a,b) packed with abnormal pleomorphic blasts (c,d), some expressing erythroid (e) and others megakaryocytic (f) antigens. (a,c) Giemsa. (b,d) H&E. (e,f) Immunoperoxidase.

Diagnostic problems

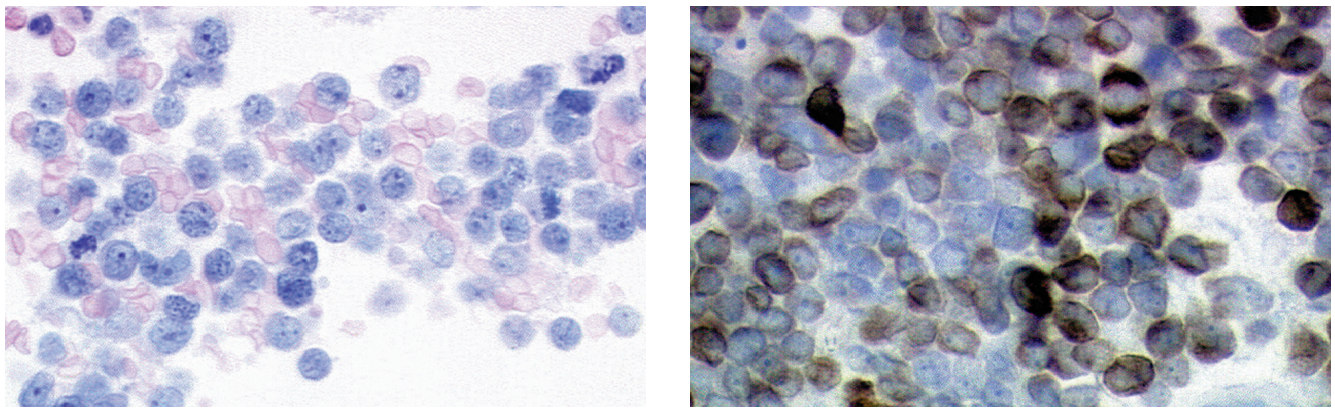
Unclassifiable cases

Leukemia is no different to most other tumor classifications with cases showing overlapping features. In the case of AML the histologist will probably not become involved in disputes over M0–M5 but occasional bizarre cases spanning M6 and M7 do occur (Fig. 7.13). In the current state of knowledge such cases do not influence therapeutic decision making.

AML or ALL

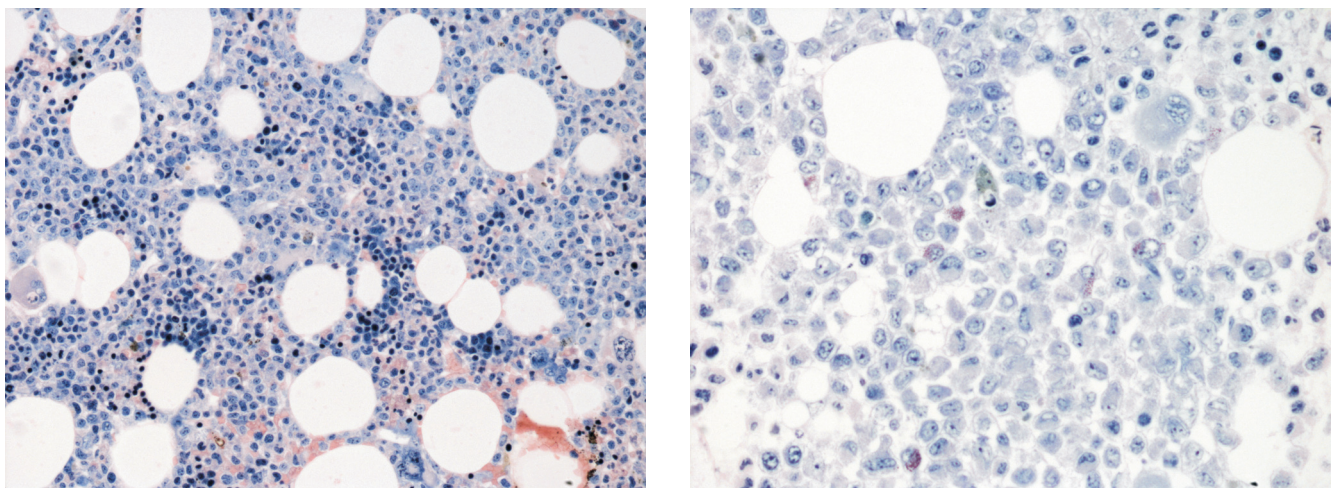
It is frequently difficult to decide on histologic grounds whether an acute leukemia is lymphoid or myeloid. Careful immunophenotyping as detailed in this chapter for AML and in Chapter 8.2 will usually resolve any difficulties (Fig. 7.14).

In some cases the pathologist needs to be cautious not to overlook those biphenotypic leukemias that express both lymphoid and myeloid markers. Fortunately, these cases are uncommon and often arise as a pre-existing leukemia relapses or transforms so that the therapeutic options are currently limited. Nevertheless, close liaison with clinical hematologists will usually result in an acceptable conclusion especially if there is a clear cytogenetic phenotype such as t(9;22) or 11q23 abnormalities, both changes known to span myeloid and lymphoid differentiation.



(a) (b)

Fig. 7.14 Case of ALL initially believed to be AML on cytologic and histologic grounds. (a) Giemsa. It was negative for all myeloid markers but expressed CD79a, a B cell antigen (b), as well as other ALL markers such as CD10.



(a) (b)

Fig. 7.15 Marrow biopsy from a patient treated with granulocyte colony-stimulating factor (GCSF) for neutropenia subsequent to chemotherapy for myeloma. This patient did not develop AML and returned to normal hematologic parameters some time afterwards.

Growth factors

The increasing use of growth factors, especially granulocyte colony-stimulating factor (GCSF), to assist patients with neutropenia after chemotherapy may cause considerable problems in marrow histology as it causes a significant increase in myeloid blast activity and can easily be mistaken for AML (Fig. 7.15). This conundrum can be completely baffling if there is evidence clinically of relapse of an underlying myeloid leukemia whose treatment has involved GCSF administration (Fig. 7.16).

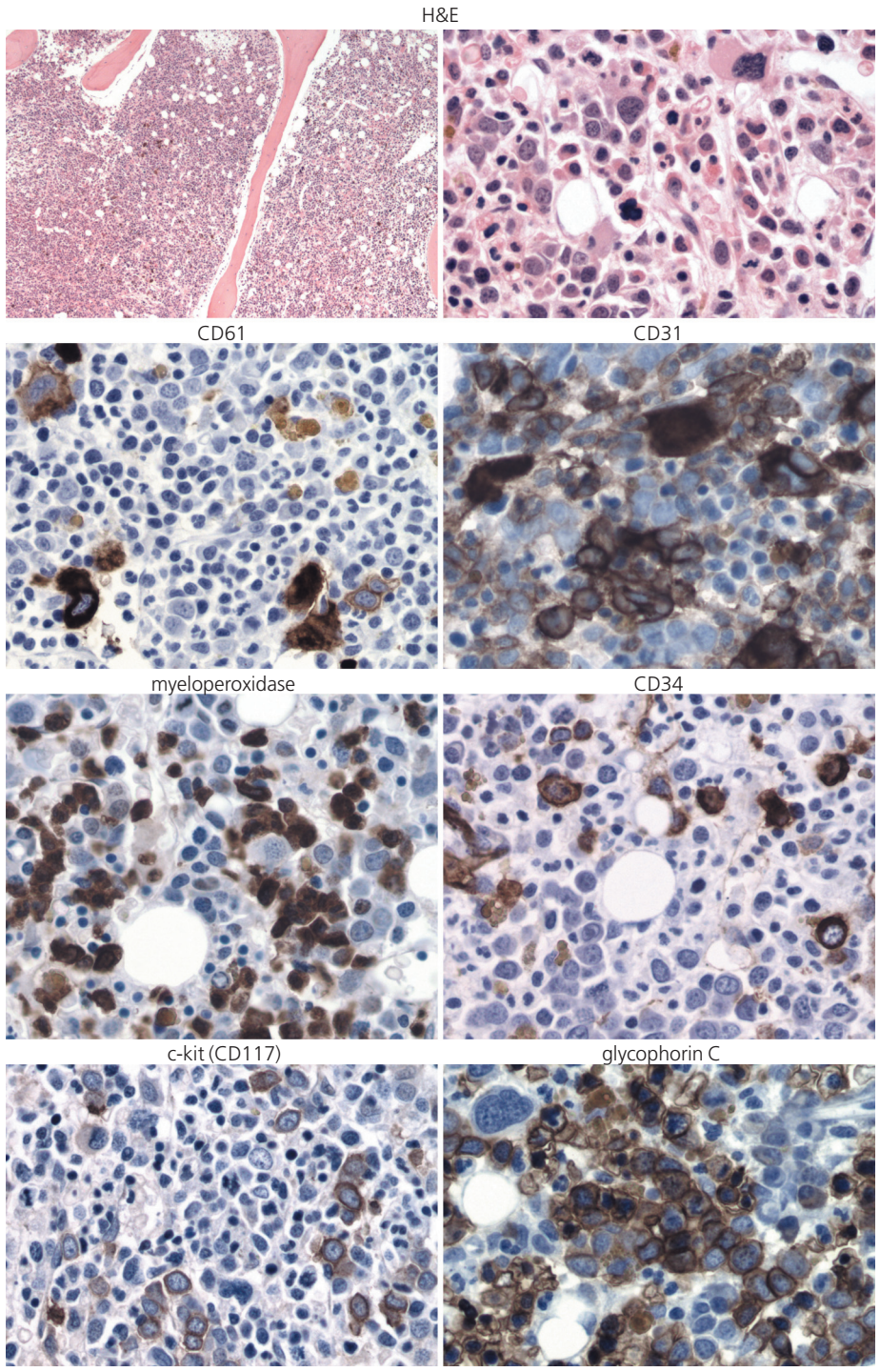
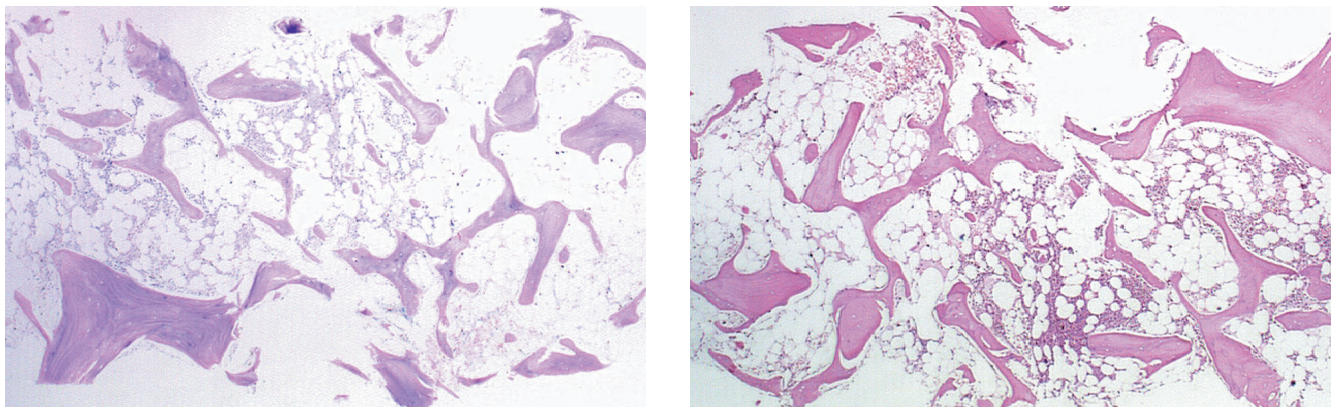


Fig. 7.16 This case illustrates the difficulty of distinguishing the blastic proliferation induced by GCSF from an underlying AML. This patient had been treated for acute megakaryoblastic leukemia with chemotherapy and GCSF. The patient became pancytopenic and blasts with complex cytogenetic abnormalities were identified. Immunophenotyping shows a complex picture suspicious of AML (e.g. c-kit [CD117] positive blasts) but not diagnostic. The patient relapsed with frank AML some weeks later.



(a) (b)

Fig. 7.17 Typical empty marrow seen a week or so after transplantation. (a) Giemsa. (b) H&E.

Acute lymphoblastic leukemia

Reflecting the histologic bias of the authors, a full presentation of this topic will be found in the chapter on lymphoma.

Transplantation and graft-versus-host disease

The place of bone marrow transplantation in the treatment of both hematologic and other malignancies is still not fully established. Many, if not most procedures, remain experimental, so close liaison with appropriate clinicians is essential in the interpretation of bone marrow and other histology from these patients. Three approaches are currently in use employing allografts, autografts and peripheral stem cell rescue. All of these employ prior intensive chemotherapy so that initial bone marrow samples are characterized by severe hypocellularity (Fig. 7.17).

The marrow regeneration is usually led by erythropoiesis followed by megakaryocytic and granulocytic proliferation (Fig. 7.18). Without too many complications the marrow regenerates steadily to produce relatively normal indices in the peripheral blood over a period of a few months. During this period the regenerating colonies can appear profoundly dysplastic which should not be misinterpreted as a recurrence of tumor (Fig. 7.19). Relapse of a leukemia or lymphoma can occur at any time even after several years and is typically dramatic (Fig. 7.20).

An early complication is failed or slow regeneration. These are being treated with a number of recombinant growth factors that themselves can produce dysplastic or bizarre appearances. Infectious complications are unfortunately common and include viral, fungal and mycobacterial diseases whose appearances are the same as those seen in other immunocompromised individuals.

The hematopathologist is often asked to diagnose acute graft-versus-host disease in skin or rectal biopsies of allograft patients. When severe the diagnosis is clinically obvious but mild cases are indistinguishable from drug-induced changes and only careful clinical review can separate these. There is now a growing consensus that mild graft-versus-host disease in allografted patients is beneficial because of an associated graft versus leukemia or lymphoma reaction (Fig. 7.21). As always, clinical correlation is necessary because immunosuppressive drugs can give an effect identical to that seen with graft-versus-host disease (Fig. 7.22).

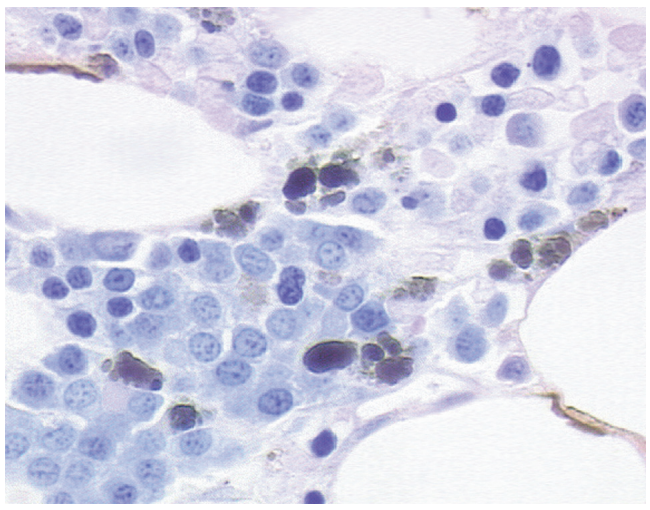
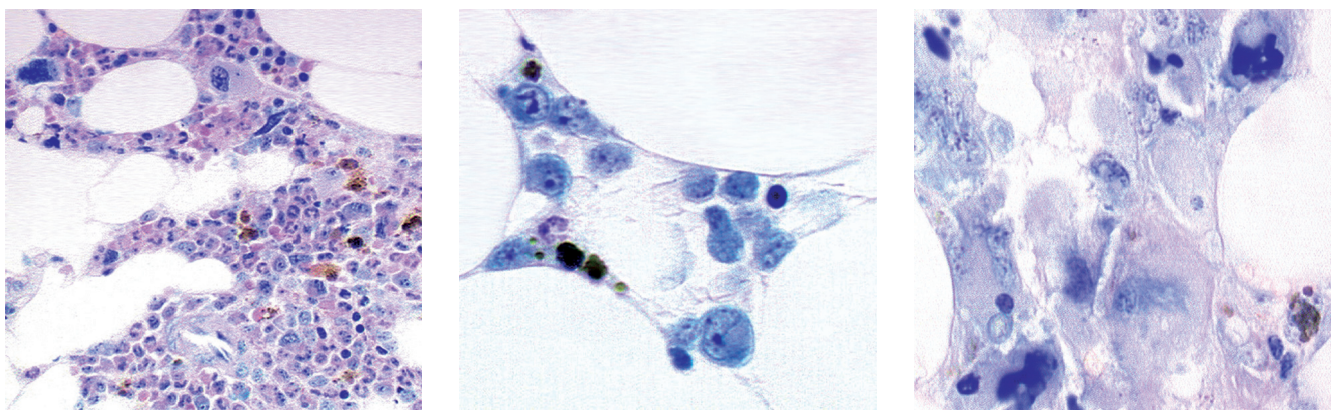
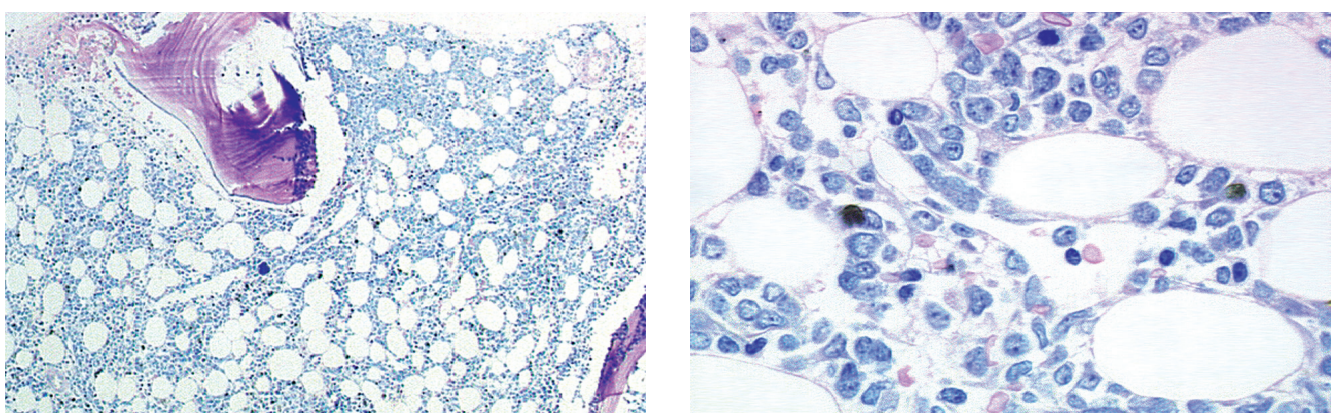


Fig. 7.18 Regenerating erythroid colonies approximately 1 month after engraftment.



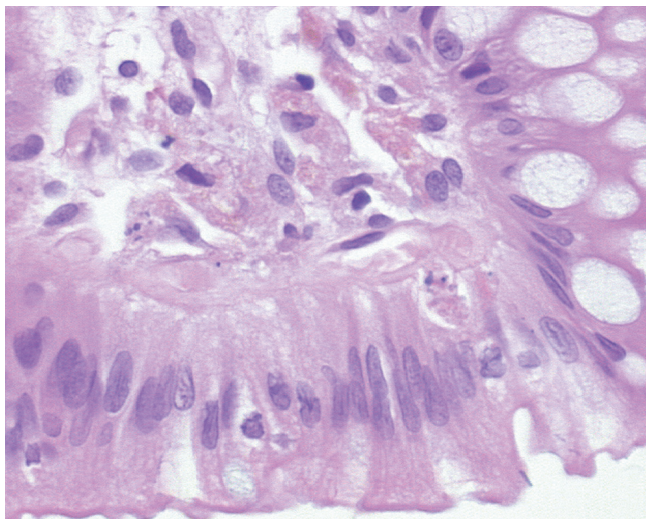
(a) (b) (c)

Fig. 7.19 Relatively normal cellularity a few months after engraftment. (a) Giemsa, but note the dysplastic erythroid cells. (b) Giemsa and megakaryocytes. (c) Giemsa, which should not be confused with leukemic relapse.

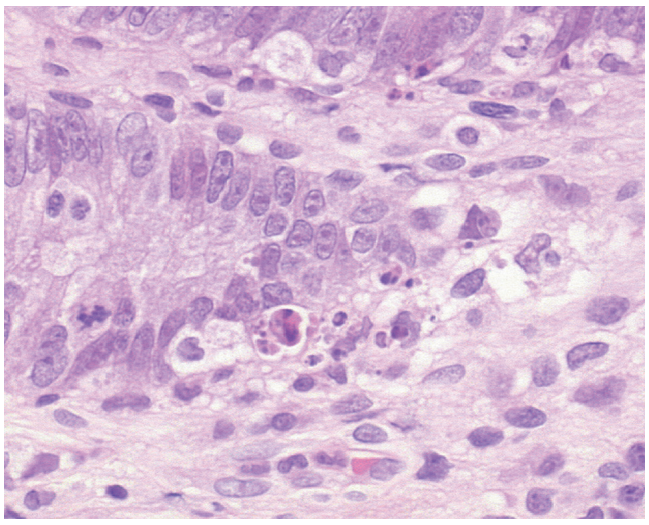


(a) (b)

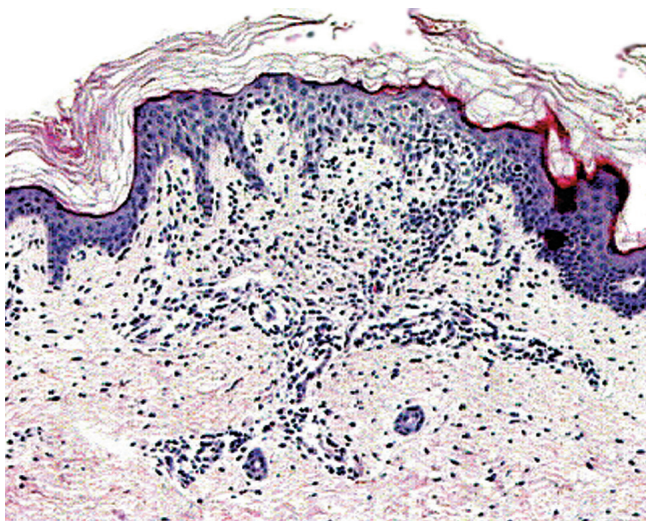
Fig. 7.20 Leukemic relapse 6 years after a successful engraftment for AML. Note that the marrow is full of primitive blast cells. (a) Low power. (b) High power. Both Giemsa.



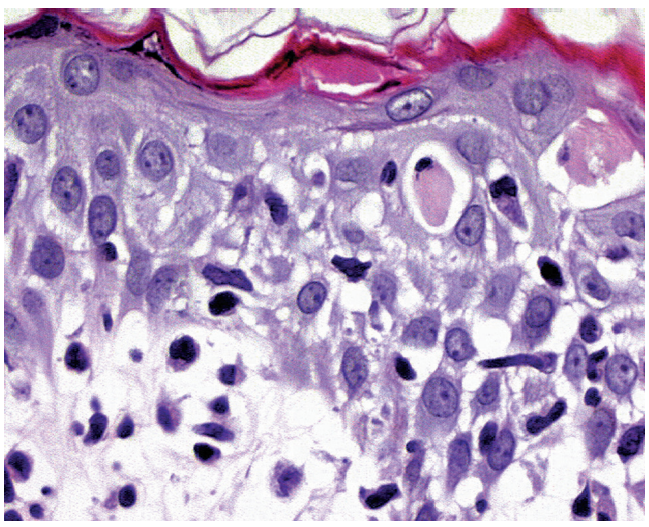
(a)



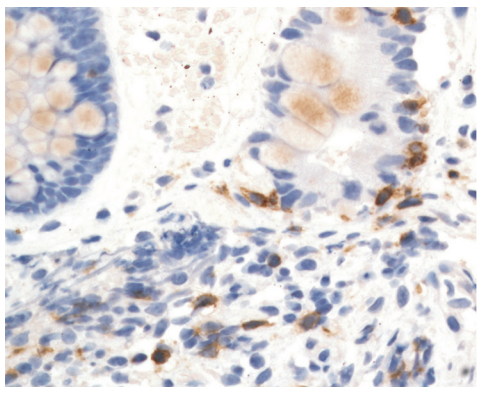
(b)



(c)



(d)



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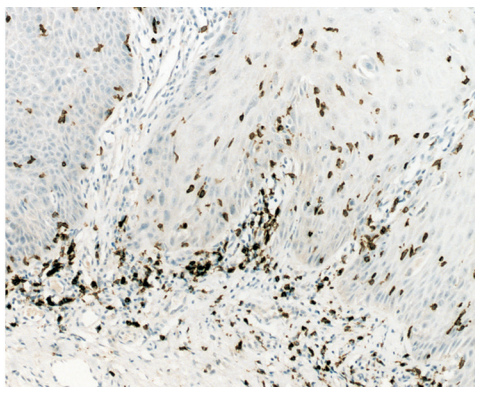
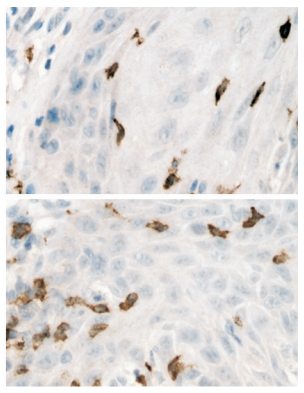
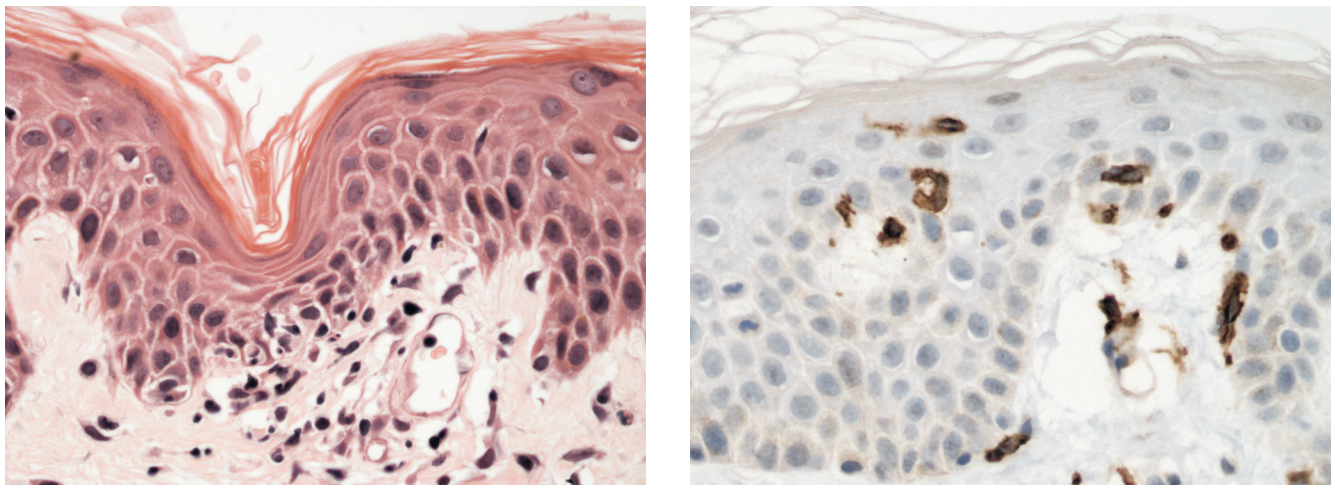


(f)



(g)

Fig. 7.21 Typical graft-versus-host disease in a bone marrow allograft recipient. (a,b) Show mild and severe involvement of rectal mucosa and (c,d) illustrate severe skin disease at low and high power. Immunostaining will highlight the infiltrating lymphocytes as T cells of CD8 subtype (e–g).



(a) (b)

Fig. 7.22 Skin biopsy from a bone marrow transplant recipient showing all of the features of graft-versus-host disease as noted in Fig. 7.21. This patient did not have clinical disease and after modification of the immunosuppresive regimen it remitted.

References

1 Bennett JM, Catovsky D, Daniel MT, *et al*. Proposals for the classification of the acute leukaemias (FAB cooperative group). *Br J Haematol* 1976; **33**: 451–8.

2 Bennett JM, Catovsky D, Daniel MT, *et al*. Proposed revised criteria for the classification of acute myeloid leukaemia. *Ann Intern Med* 1985; **103**: 626–9.