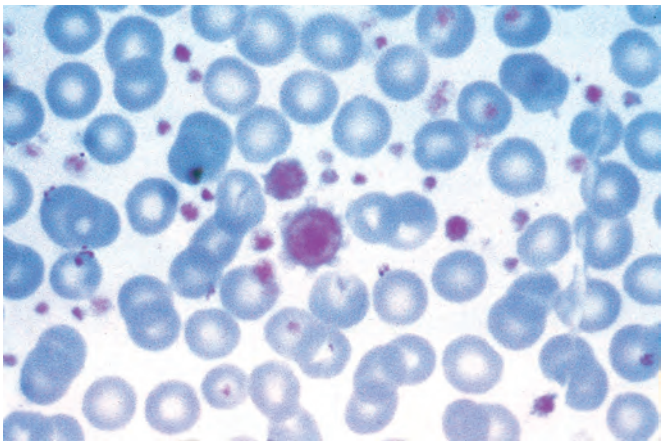

Figure 13-36 Essential thrombocytosis. Peripheral blood smear shows marked thrombocytosis, including giant platelets approximating the size of surrounding red cells.

number and include abnormally large forms. Delicate reticulin fibrils are often seen, but the overt fibrosis of primary myelofibrosis (see later) is absent. Peripheral smears usually reveal abnormally large platelets (Fig. 13-36), often accompanied by mild leukocytosis. Modest degrees of extramedullary hematopoiesis may occur, producing mild organomegaly in about 50% of patients. Uncommonly, a spent phase of marrow fibrosis or transformation to AML supervenes.

The incidence of ET is 1 to 3 per 100,000 per year. It usually occurs past the age of 60 but may also be seen in young adults. Dysfunctions of platelets derived from the neoplastic clone can lead to thrombosis and hemorrhage, the major clinical manifestations. Platelets are not only increased in numbers but also frequently demonstrate qualitative abnormalities in functional tests. The types of thrombotic events resemble those observed in PCV; they include deep venous thrombosis, portal and hepatic vein thrombosis, and myocardial infarction. One characteristic symptom is *erythromelalgia*, a throbbing and burning of hands and feet caused by occlusion of small arterioles by platelet aggregates, which may also be seen in PCV.

ET is an indolent disorder with long asymptomatic periods punctuated by occasional thrombotic or hemorrhagic crises. Median survival times are 12 to 15 years. Thrombotic complications are most likely in patients with very high platelet counts and homozygous *JAK2* mutations. Therapy consists of "gentle" chemotherapeutic agents that suppress thrombopoiesis.

Primary Myelofibrosis

The hallmark of primary myelofibrosis is the development of obliterative marrow fibrosis. The replacement of the marrow by fibrous tissue reduces bone marrow hematopoiesis, leading to cytopenias and extensive extramedullary hematopoiesis. Histologically, the appearance is identical to the spent phase that occurs occasionally late in the course of other myeloproliferative disorders. This similarity also extends to the underlying pathogenesis.

Activating JAK2 mutations are present in 50% to 60% of cases and activating MPL mutations in an additional 1% to 5% of cases of primary myelofibrosis. As with ET, most of the remaining cases have been recently observed to have mutations in calreticulin that are hypothesized to give rise to increased JAK-STAT signaling.

The chief pathologic feature is the extensive deposition of collagen in the marrow by non-neoplastic fibroblasts. The fibrosis inexorably displaces hematopoietic elements, including stem cells, from the marrow and eventually leads to marrow failure. It is probably caused by the inappropriate release of fibrogenic factors from neoplastic megakaryocytes. Two factors synthesized by megakaryocytes have been implicated: *platelet-derived growth factor* and *TGF-β*. As you recall, platelet-derived growth factor and TGF-β are fibroblast mitogens. In addition, TGF-β promotes collagen deposition and causes angiogenesis, both of which are observed in myelofibrosis.

As marrow fibrosis progresses, circulating hematopoietic stem cells take up residence in niches in secondary hematopoietic organs, such as the spleen, the liver, and the lymph nodes, leading to the appearance of extramedullary hematopoiesis. For incompletely understood reasons, red cell production at extramedullary sites is disordered. This factor and the concomitant suppression of marrow function result in moderate to severe anemia. It is not clear whether primary myelofibrosis is truly distinct from PCV and ET, or merely reflects unusually rapid progression to the spent phase.

MORPHOLOGY

Early in the course, the marrow is often hypercellular due to increases in maturing cells of all lineages, a feature reminiscent of PCV. Morphologically, the erythroid and granulocytic precursors appear normal, but megakaryocytes are large, dysplastic, and abnormally clustered. At this stage fibrosis is minimal, and the blood may show leukocytosis and thrombocytosis. **With progression, the marrow becomes more hypocellular and diffusely fibrotic.** Clusters of atypical megakaryocytes with unusual nuclear shapes (described as "cloud-like") are seen, and hematopoietic elements are often found within dilated sinusoids, which is a manifestation of severe architectural distortion cause by the fibrosis. Very late in the course, the fibrotic marrow space may be converted into bone, a change called "osteosclerosis." These features are identical to those seen in the spent phase of other myeloproliferative disorders.

Fibrotic obliteration of the marrow space leads to extensive extramedullary hematopoiesis, principally in the spleen, which is usually markedly enlarged, sometimes up to 4000 gm. Grossly, such spleens are firm and diffusely red to gray. As in CML, subcapsular infarcts are common (see Fig. 13-40). Initially, extramedullary hematopoiesis is confined to the sinusoids, but later it expands into the cords. The liver may be enlarged moderately by sinusoidal foci of extramedullary hematopoiesis. Hematopoiesis can also appear within lymph nodes, but significant lymphadenopathy is uncommon.

The marrow fibrosis is reflected in several characteristic blood findings (Fig. 13-37). Marrow distortion leads to the premature release of nucleated erythroid and early granulocyte progenitors (**leukoerythroblastosis**), and immature cells also enter the circulation from sites of extramedullary hematopoiesis. **Teardrop-shaped red cells** (dacryocytes), cells that were probably damaged during the birthing process in the fibrotic marrow, are also often seen. Although characteristic of primary