prothrombotic state) must be involved in triggering full-blown TTP.

For unknown reasons, in TTP, central nervous system involvement is the dominant feature, whereas renal involvement is seen in about 50% of patients. The clinical findings are dictated by the distribution of the microthrombi, which are found in arterioles throughout the body. With plasma exchange, which removes autoantibodies and provides functional ADAMTS13, TTP (which once was uniformly fatal) can be treated successfully in more than 80% of patients.

## MORPHOLOGY

The morphologic findings in the various forms of HUS/TTP show considerable overlap, and vary mainly according to chronicity rather than cause. In acute, active disease the kidney may show patchy or diffuse cortical necrosis (described later) and subcapsular petechiae. On microscopic examination, the glomerular capillaries are occluded by thrombi composed of aggregated platelets and to a lesser extent fibrin. The capillary walls are thickened due to endothelial cell swelling and subendothelial deposits of cell debris and fibrin. Disruption of the mesangial matrix and damage to the mesangial cells often results in mesangiolysis. Interlobular arteries and arterioles often show fibrinoid necrosis of the wall and occlusive thrombi. Chronic disease is confined to patients with atypical HUS or TTP, and has features that stem from continued injury and attempts at healing. The renal cortex reveals various degrees of scarring. By light microscopy the glomeruli are mildly hypercellular and have marked thickening of the capillary walls associated with splitting or reduplication of the basement membrane (so called double contours or tram tracks). The walls of arteries and arterioles often exhibit increased layers of cells and connective tissue ("onion-skinning") that narrow the vessel lumens. These changes lead to persistent hypoperfusion and ischemic atrophy of the parenchyma, which manifests clinically as renal failure and hypertension.

## KEY CONCEPTS

### Thrombotic Microangiopathy

- Thrombotic microangiopathy encompasses a diverse set of conditions that all lead to platelet activation and deposition of thrombi in the microvasculature, accompanied by red cell hemolysis, tissue ischemia and organ dysfunction, and a consumptive thrombocytopenia.
- In typical HUS, Shiga-like toxin produced by bacteria, most commonly *E. coli* strain O157:H7, is responsible for producing platelet activation and thrombosis.
- In most cases of atypical HUS, aberration activation of complement due to inherited mutations or acquired autoantibodies is the key pathogenic abnormality.
- In TTP, deficiencies of ADAMTS13, a negative regulator of vWF, permits the formation of abnormally large multimers of vWF that are capable of activating platelets.

## Other Vascular Disorders

### *Atherosclerotic Ischemic Renal Disease*

We have seen that atherosclerotic unilateral renal artery stenosis can lead to hypertension. *Bilateral renal artery disease*, usually diagnosed definitively by arteriography, is a fairly common cause of chronic ischemia with renal insufficiency in older individuals, sometimes in the absence of hypertension. The importance of recognizing this condition is that surgical revascularization can prevent further decline in renal function.

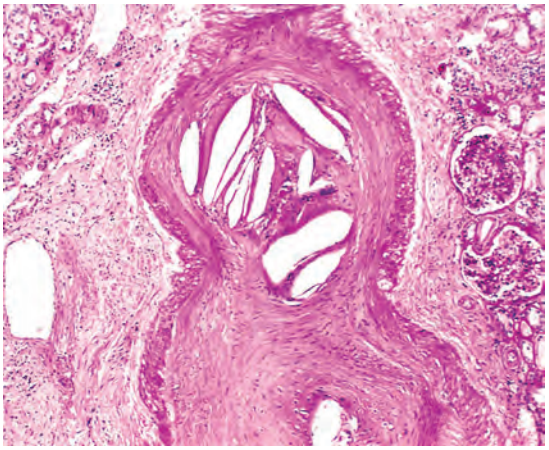

**Figure 20-41** Atheroemboli with typical cholesterol clefts in an interlobar artery.

### *Atheroembolic Renal Disease*

Embolization of fragments of atheromatous plaques from the aorta or renal artery into intrarenal vessels occurs in older adults with severe atherosclerosis, especially after surgery on the abdominal aorta, aortography, or intra-aortic cannulization. These emboli can be recognized in the lumens of arcuate and interlobular arteries by their content of cholesterol crystals, which appear as rhomboid clefts (Fig. 20-41). The clinical consequences of atheroemboli vary according to the number of emboli and the preexisting state of renal function. Frequently they are of no significance. However, acute renal injury or failure may develop in older adults in whom renal function is already compromised.

### *Sickle-Cell Nephropathy*

Sickle-cell disease (homozygous) or trait (heterozygous) may lead to a variety of alterations in renal morphology and function, some of which produce clinically significant abnormalities. The various manifestations are grouped under *sickle-cell nephropathy*.

The most common abnormalities are *hematuria* and a *diminished concentrating ability* (hyposthenuria). These are thought to be due to accelerated sickling in the hypertonic hypoxic milieu of the renal medulla; the hyperosmolarity dehydrates red cells and increases intracellular HbS concentrations, which likely explains why even those with sickle trait are affected. Patchy *papillary necrosis* may occur in both homozygotes and heterozygotes; this is sometimes associated with cortical scarring. *Proteinuria* is also common in sickle-cell disease, occurring in about 30% of patients. It is usually mild to moderate, but on occasion the overt nephrotic syndrome arises, associated with sclerosing glomerular lesions.