ANGIOSARCOMA OF THE LIVER

A guide for histopathologists

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Foreword

From a medical point of view the first discovery of a link between exposure to a chemical and an occupational disease is an interesting process, especially when this disease is a very rare cancer. A good example is when the possible link between vinyl chloride monomer (VCM) and angiosarcoma of the liver was first described. Afterwards the causal relationship between occupational exposure to VCM and angiosarcoma of the liver was proven by a lot of studies.

Important is that industry in this process has taken its responsibility by initiating several studies. One of the many initiatives was to start and conduct a worldwide Register of cases of angiosarcoma associated with the production of vinyl chloride monomer and polyvinyl chloride. The Medical Committee within the European Council of Vinyl Manufacturers (ECVM) maintains this Register as a voluntary product stewardship undertaking. Though this case series cannot be considered complete, the Register is an effort to supplement the scientific research on the relationship between angiosarcoma of the liver and exposure to VCM.

Being aware of the rarity of angiosarcoma of the liver, the ECVM Medical Committee launched the idea of developing a guide for histopathologists to help them in diagnosis.
It was a great pleasure for us that professor P.P.Anthony, dr. B. Bancel and dr. N. S Dallimore were willing to accept this challenge. Their professional competence, experience and never-ending enthusiasm have greatly facilitated the creation of this booklet. Our sincere gratitude goes to them for devoting their precious time to this booklet for their colleagues.

We hope that the users of this guide will inform us of any angiosarcoma of the liver due to exposure to VCM, for which we are already thanking them.

Marc Boeckx
Occupational Physician
Chairman of the ECVM Medical Committee

DEFINITION

The World Health Organization International Classification of Tumours of the Liver defines angiosarcoma as "a malignant tumour composed of spindle or pleomorphic cells that line, or grow into, the lumina of pre-existing vascular spaces such as liver sinusoids and small veins". The terms haemangiosarcoma, malignant haemangioendothelioma and Kupffer cell sarcoma have been used in the past; the latter term is incorrect as the tumour does not originate from Kupffer cells.

INCIDENCE, AGE AND SEX

Angiosarcoma of the liver is rare but it is the commonest sarcoma at this site. A survey covering Great Britain identified only 35 cases during a 15 year period. A similar study from the United States showed an annual incidence of 0.14-0.25 per million. Somewhat higher figures have been reported from Portugal, Germany and Japan.   Large scale studies by expert panels have indicated a high rate of diagnostic error due to the variable histological appearances of the tumour. Immunocytochemistry for the demonstration of endothelial and other antigenic markers has made recognition easier during recent years. The peak age incidence is in the sixth and seventh decades of life and the male to female ratio is 3 to 1.

CLINICAL PRESENTATION, LABORATORY AND IMAGING
STUDIES AND OUTCOME

Patients usually present with advanced disease evidenced by right upper quadrant abdominal pain, anorexia, nausea, weight loss, fever, hepatomegaly and ascites. Less common manifestations include haemoperitoneum due to rupture of the tumour, distant metastases and various haematological disorders such as disseminated intravascular coagulopathy. Terminal jaundice develops in half to two-thirds of cases.

Laboratory abnormalities include anaemia which may be of the microangiopathic haemolytic type, leukocytosis or leukopenia, thrombocytopenia and sometimes all these together, i.e. pancytopenia. Tests of hepatic function show elevated aminotransferase levels, prolonged prothrombin time and a raised alkaline phosphatase. Plain x-ray film of the abdomen shows opacification of liver, spleen and lymph nodes in cases associated with thorium dioxide (Thorotrast).

Angiography shows a diffusely abnormal vascular pattern and hepatic isotope scans, computed tomography and magnetic resonance imaging demonstrate tumour-like abnormalities. Definitive diagnosis requires a liver biopsy.

Surgical excision is generally not feasible. The majority of patients die within 2-3 months after diagnosis. Prolongation of survival has been achieved in some cases by chemo/ radiotherapy.

AETIOLOGY

Although there are well established causes of angiosarcoma of the liver, the majority of cases have no known aetiology.

Thorium dioxide (Thorotrast)

The best known aetiological agent is Thorotrast, a radiological contrast medium. This was much in use from the late 1920's to the mid-1950's, especially for the angiographic investigation of suspected intracranial abnormalities. Thorium is radioactive, emitting short range alpha radiation. The biological half-life is approximately 400 years. Seventy per cent of the injected dose is taken up by the liver, 20% by the spleen and 10% by the bone marrow; none of it is eliminated thereafter. In the mid-1970's, some 50-100,000 people were estimated to be at risk and the incubation period is long, 15-25 years or more. In recent years, an increasing number of bile duct and hepatocellular carcinomas have been reported. In a minority of cases, portal hypertension without splenomegaly may be seen before the tumour develops.

Vinyl chloride monomer (VCM)

The ill-effects of exposure to VCM during the manufacture of polyvinyl chloride (PVC) has raised concern from the 1960's onwards. The maximum risk occurs when workers enter autoclaves in which VCM has been polymerized to PVC. Manual cleaning releases trapped VCM in a gaseous form. High levels of 250-10,000 ppm may be reached in the air during this process. Acute toxicity is manifested by impaired consciousness as the gas is narcotic. Repeated exposure leads to scleroderma-like changes in skin, Raynaud's phenomenon, acral osteolysis and portal hypertension with splenomegaly. Safety measures were introduced in the 1970's and the maximum level of exposure was

reduced to 10 ppm. The maximum level of exposure further diminished to 3 ppm in the EU, but a lot of countries in the EU and in the USA accepted an occupational exposure level of 1 ppm. As with Thorotrast, angiosarcoma of the liver develops late, after 25 years or more. A few cases of hepatocellular carcinoma have been reported in workers exposed to VCM but not bile duct carcinoma. In the 1980's it was estimated that 200-1,200 cases of angiosarcoma would occur in Western Europe and 3-400 in the United States over the next 30 years but this proved to be an overestimate. However, the situation elsewhere may well be different.

Arsenic and other agents

Chronic arsenic intoxication has been known for many years to produce angiosarcoma of the liver both as an occupational hazard amongst vintners and as an iatrogenic effect in patients taking the once popular dermatological remedy, Fowler's solution. Other suggested aetiologies include androgenic/anabolic steroids, oral contraceptive agents, copper sulphate spray, pesticides and radiation but the evidence for these is weak.

LIVER CHANGES PRECEDING THE DEVELOPMENT OF ANGIOSARCOMA

These have been well studied both in experimental animals and in man and are remarkably similar, regardless of aetiology, i.e. they are the same in cases due to Thorotrast, VCM or arsenic or indeed in those in which there is no known aetiology. The changes are illustrated in Figs 1-6. They range from sinusoidal dilatation, endothelial cell hyperplasia, doubling of liver cell plates with nuclear variability (small/large cell dysplasia) to fibrosis that is initially perisinusoidal and later portal/periportal and subcapsular. Ultimately, cirrhosis may develop. The most striking changes are those seen in endothelial cell nuclei. These enlarge, become irregular and hyperchromatic (endothelial cell dysplasia) and the distinction from overt malignancy becomes difficult. Thorotrast deposits are readily recognized as slightly refractile, grey-brown granules in portal tracts and under Glisson's capsule. They can be illuminated by phase contrast microscopy and specifically identified by energy dispersive x-ray microanalysis. Auto-radiography identifies the alpha emissions as short, dotted tracks.

MACROSCOPIC APPEARANCES

At autopsy, the liver is extensively involved by ill-defined, spongy, haemorrhagic nodules and yellowish-white areas of scarring (Fig. 7). Thrombosis and infarction are common. Large cavities filled with blood may be seen and these may have ruptured giving rise to intraperitoneal haemorrhage. A reticular pattern of fibrosis, best seen on the capsular surface, may still be evident. Metastases are present in about one fifth of cases, usually in lymph nodes, spleen, lungs, bone or adrenals. In cases associated with Thorotrast, the spleen is often small and atrophic, unless enlarged by tumour.

MICROSCOPIC APPEARANCES

Angiosarcoma of the liver is composed of malignant endothelial cells of variable appearance. Most frequently, they are elongated, spindle shaped or pleomorphic but, occasionally, they may be round (Figs. 8-10). The nuclei are hyperchromatic and the cytoplasm is pale, eosinophilic and ill-defined. Mitotic figures are frequent.

The tumour grows in pre-existing vascular spaces such as sinusoids and veins. The most characteristic feature is a scaffold-like or tectorial pattern of growth in which tumour cells line the surface of liver cell plates. This is particularly evident when the sinusoidal spaces are dilated (Fig. 11). The liver cell plates eventually atrophy underneath their covering of tumour cells (Fig. 12). In the end, fibrous masses form which contain irregular channels lined by tumour cells (Fig. 13) or else these coalesce into large cavernous spaces containing papillary fronds (Fig. 14). Peliosis-like blood filled spaces may disrupt the liver in which tumour cells may be difficult to find (Fig. 15). Tumour cells may also be few in areas of scarring (Fig. 16). These different patterns frequently co-exist.

The most difficult diagnostic problem, especially when only a limited amount of tissue is available, arises when the tumour consists only of solid masses of spindle cells (Fig. 17). This cannot be distinguished from fibrosarcoma or leiomyosarcoma on an HE section alone (see differential diagnosis).

A minority of angiosarcomas contain islands of extramedullary haemopoiesis (Fig. 18) or, even less commonly, show erythrophagocytosis by tumour cells (Fig. 19).

Conventional special stains are of little value in the diagnosis of angiosarcoma of the liver but a reticulin stain characteristically shows the laying down of fibrillary material in sinusoids, initially in Disse's space and later in the lumina, leading to their obliteration (Fig. 20).

DIFFERENTIAL DIAGNOSIS

The diagnosis should not be difficult at autopsy, provided that a reasonable number of tissue blocks is taken from all parts of the liver that show different appearances: haemorrhagic, solid and fibrous. Characteristic appearances will then be seen in one or more of these samples.

Needle biopsy diagnosis can be a problem especially when there is much necrosis, heavy scarring and/or tumour cells are few (Fig. 16) and when the tumour appears to be papillary (Fig. 14) or consists entirely of solid and spindle cells (Fig. 17).

Immunocytochemistry

Immunocytochemistry has largely resolved these problems as the cells of angiosarcoma can be shown to be of endothelial origin. The most useful antibodies are those raised against CD31 and CD34 cluster antigens and Factor VIII related antigen (von Willebrand factor) (Figs. 21, 22). CD31 and CD34 reactions are rather more sensitive than those with Factor VIII related antigen/von Willebrand factor but are less specific.

Histochemistry

Lectin histochemistry, a non-immune reaction, can also be useful. Ulex Europaeus lectin binds to endothelia and is a sensitive method. The result should always be checked against that shown by epithelial structures in the tissue sample, particularly bile ducts. Ulex Europaeus binds to the H substance of blood group O secretor individuals which is expressed by biliary epithelial cells.
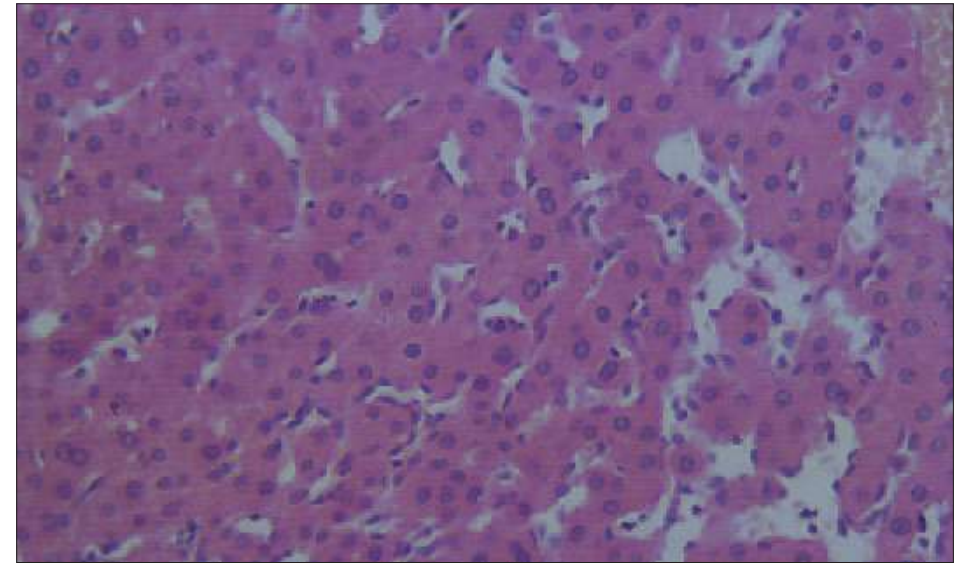
Figure 1/ Focal sinusoidal dilatation, endothelial cell hyperplasia and double liver cell plates with mild nuclear variability.
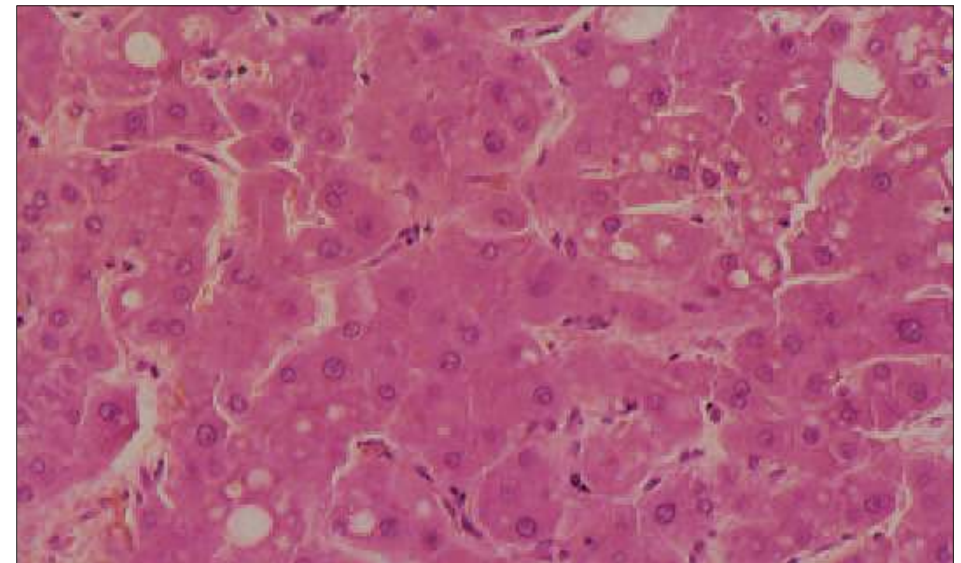
Figure 2/ Enlarged liver cells in thick plates. The sinusoidal lining is prominent. Endothelial cell nuclei are irregularly shaped and hyperchromatic.
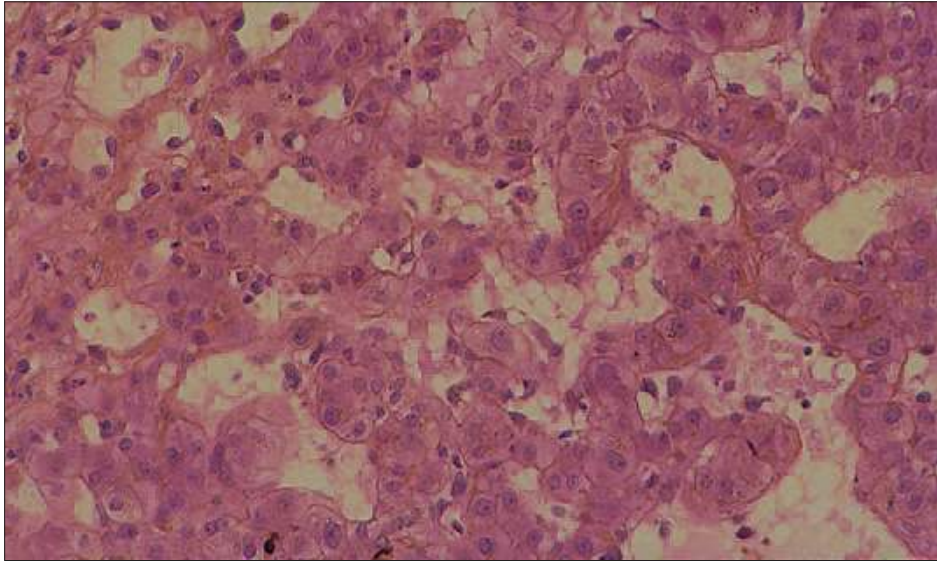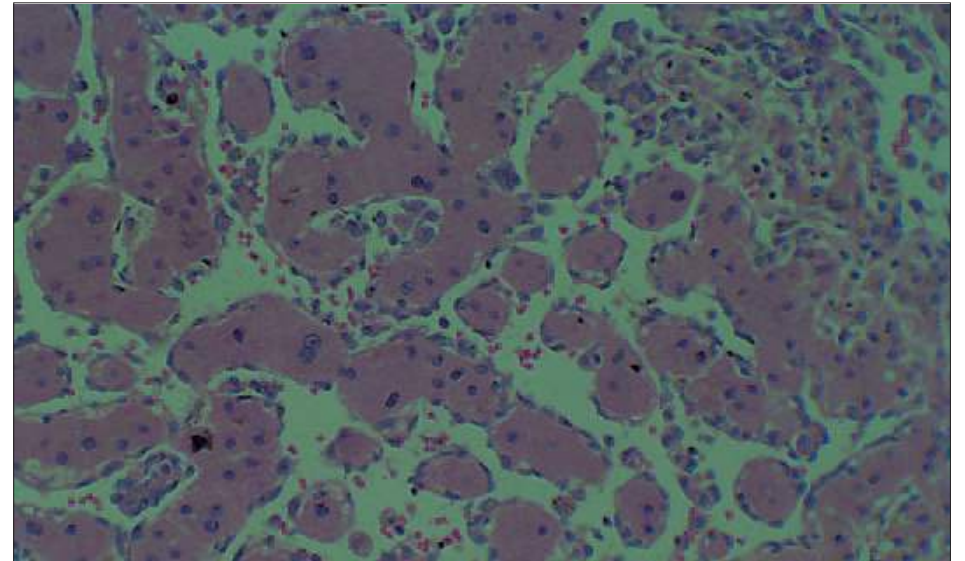
Figure 3/ Marked endothelial cell dysplasia with sinusoidal dilatation and liver cell dysplasia.
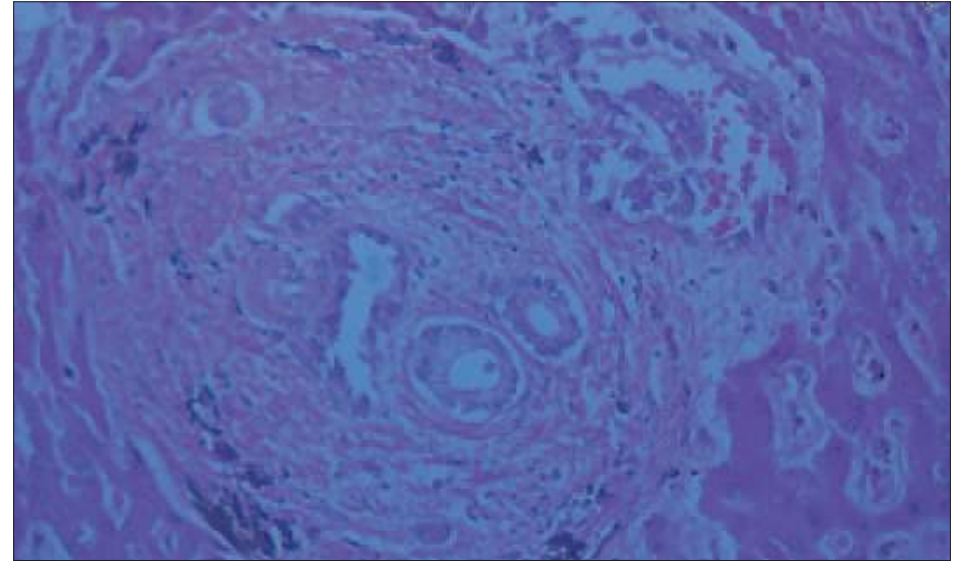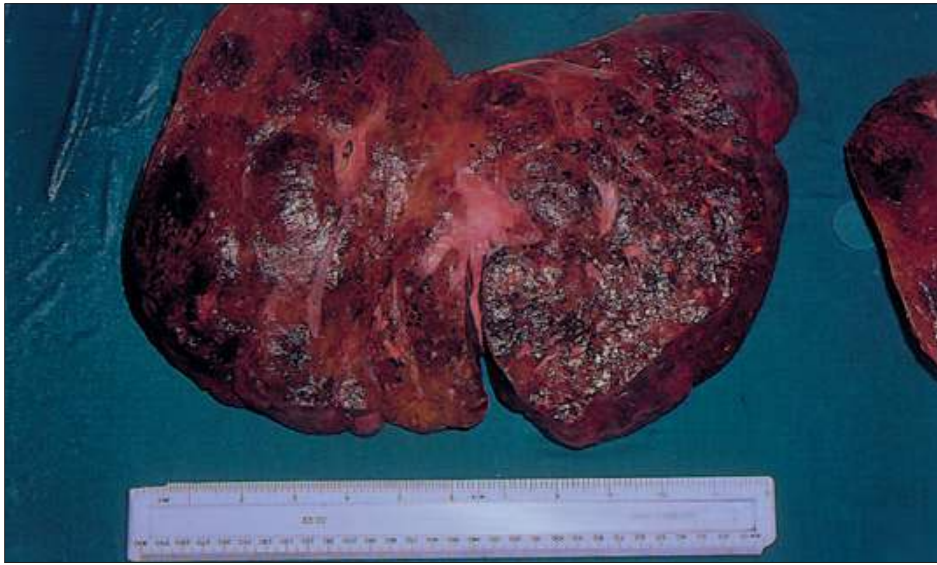

**Figure 5/** Enlarged portal tract containing grey-brown granules of Thorotrast.
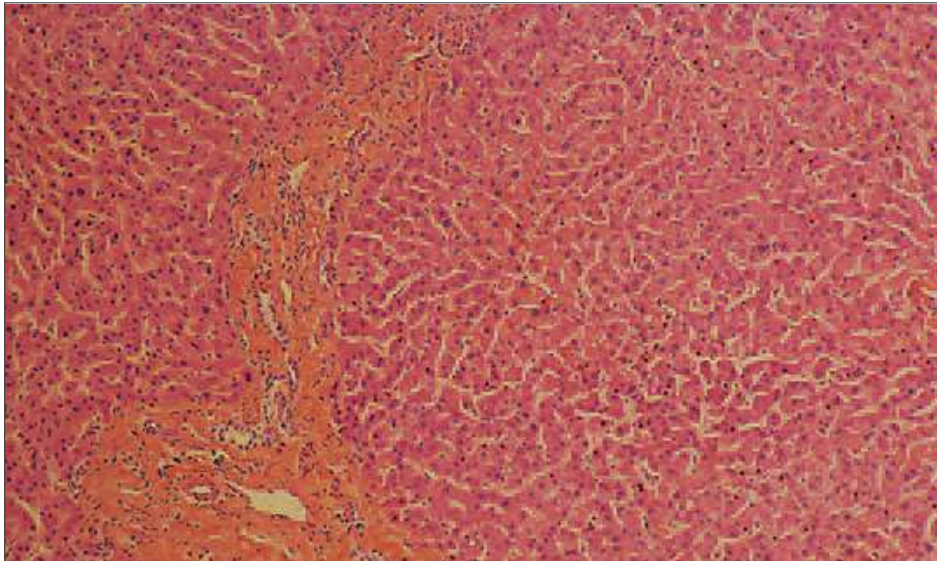
**Figure 4/** Portal/periportal fibrosis.

Figure 6/ The degree of endothelial hyperplasia and the nuclear abnormalities of the cells are too severe in this instance and the changes must be considered to be truly neoplastic. Indeed, obvious angiosarcoma is seen in the upper right corner.

Figure 7/ Angiosarcoma of the liver induced by VCM. The cut surface is mottled, haemorrhagic and shows ill defined scarring. Part of the spleen is shown on the right. This, too, contains tumour.
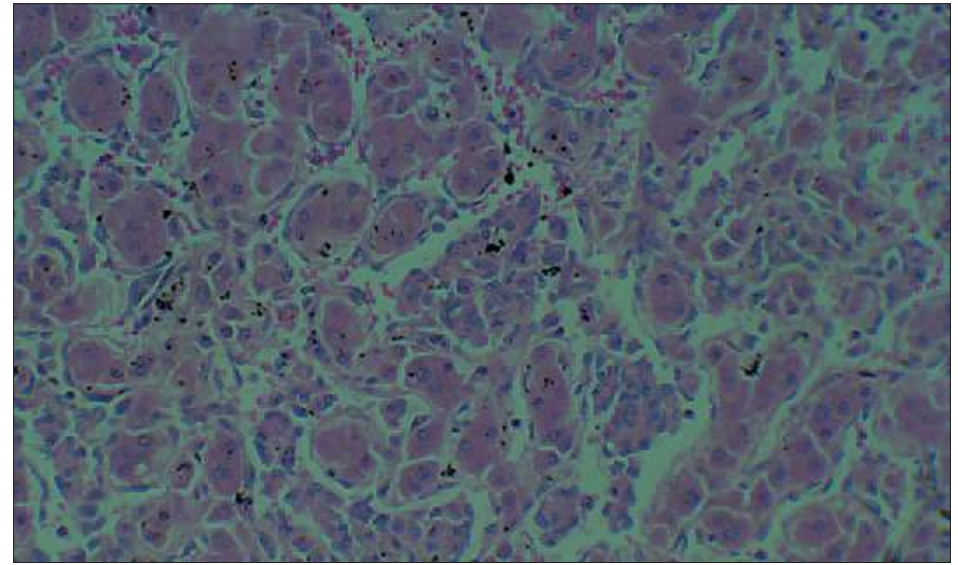
Figure 9/ The sinusoidal growth pattern is more evident. Tumour cells form clumps in the lumina.
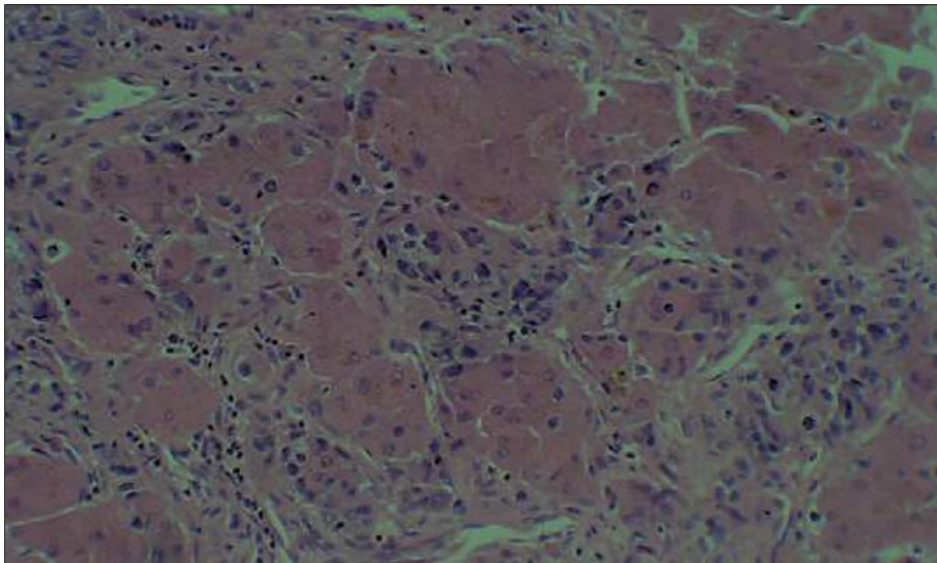
Figure 8/ Liver sinusoids are filled with oval, spindle and pleomorphic cells with hyperchromatic nuclei.
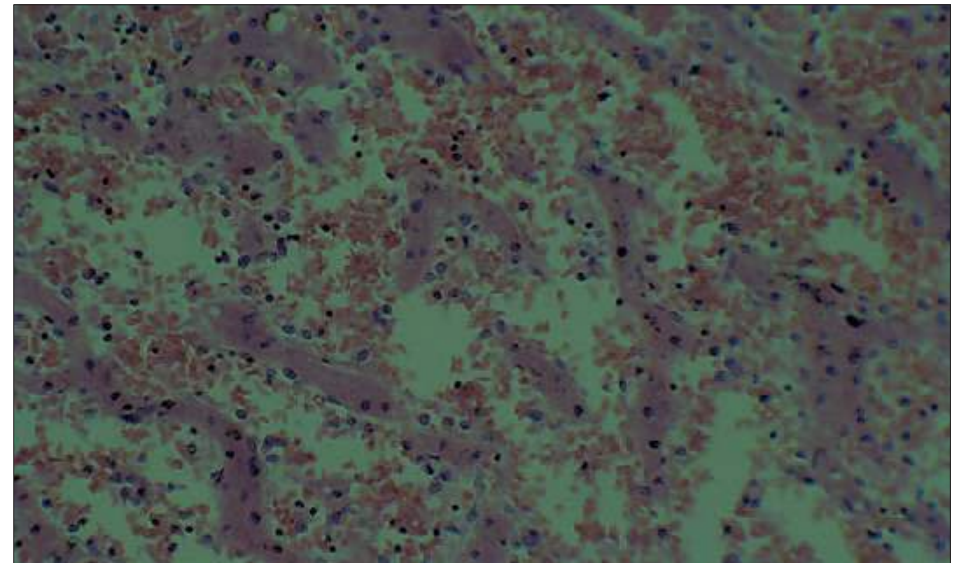
Figure 10/ The sinusoids are widely dilated and contain few, rounded tumour cells mixed with blood.
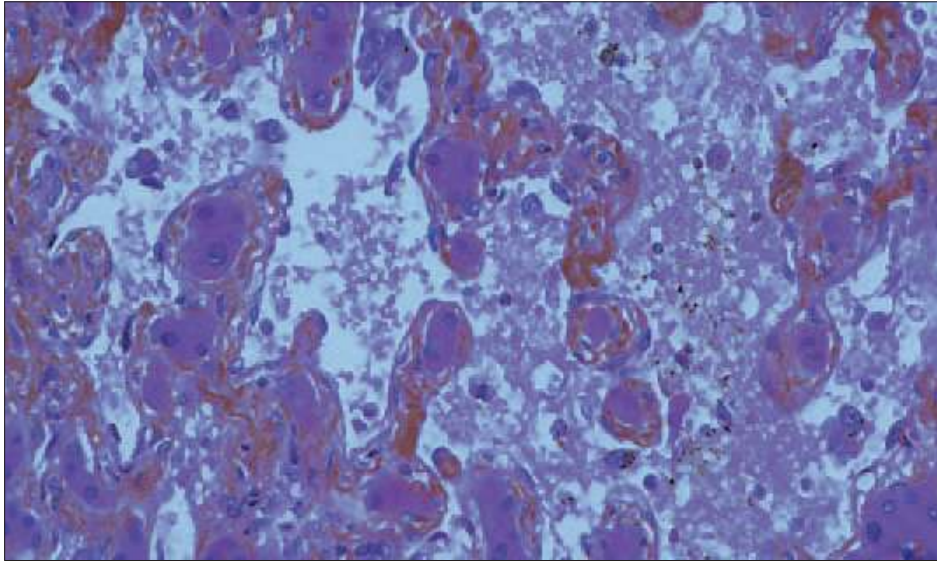
Figure 11/ *Widely dilated sinusoids in which tumour cells line the surface of liver cells in a scaffold-like or tectorial manner.*
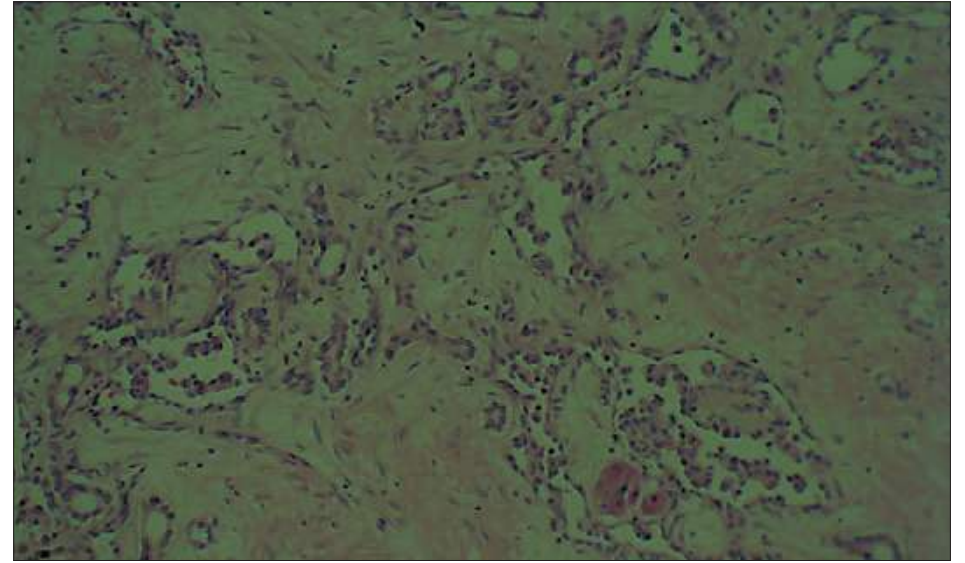
Figure 13/ *Irregular, interconnected vascular channels set in an area of fibrosis. The channels are lined by layers of tumour cells. A few liver cells can still be identified in the lower right corner of the field.*
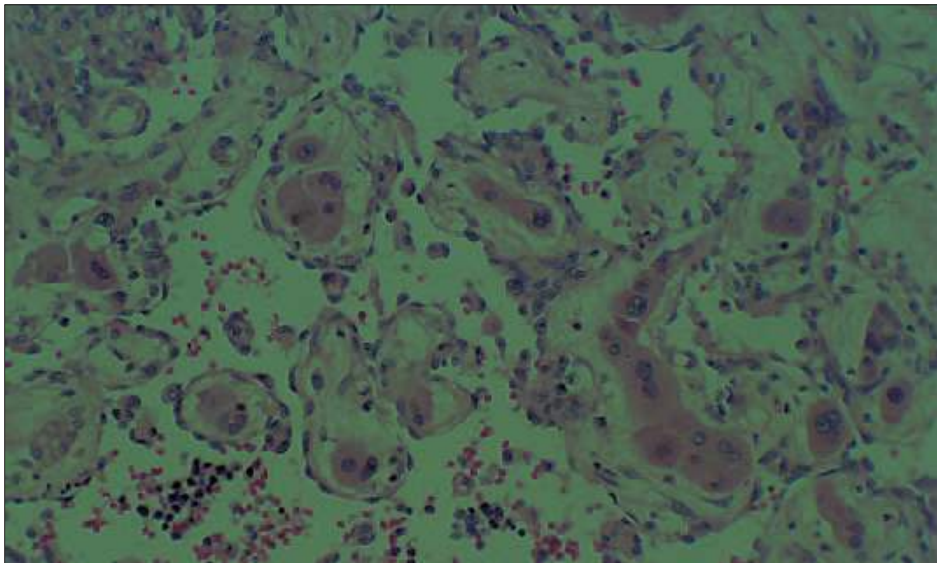
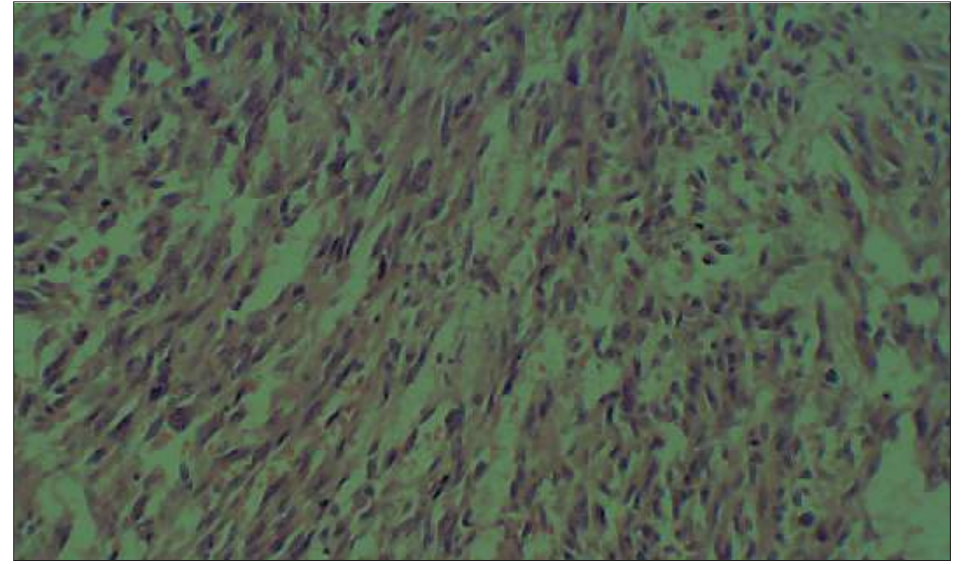**Figure 12/** *Liver cell plates undergoing atrophy.*
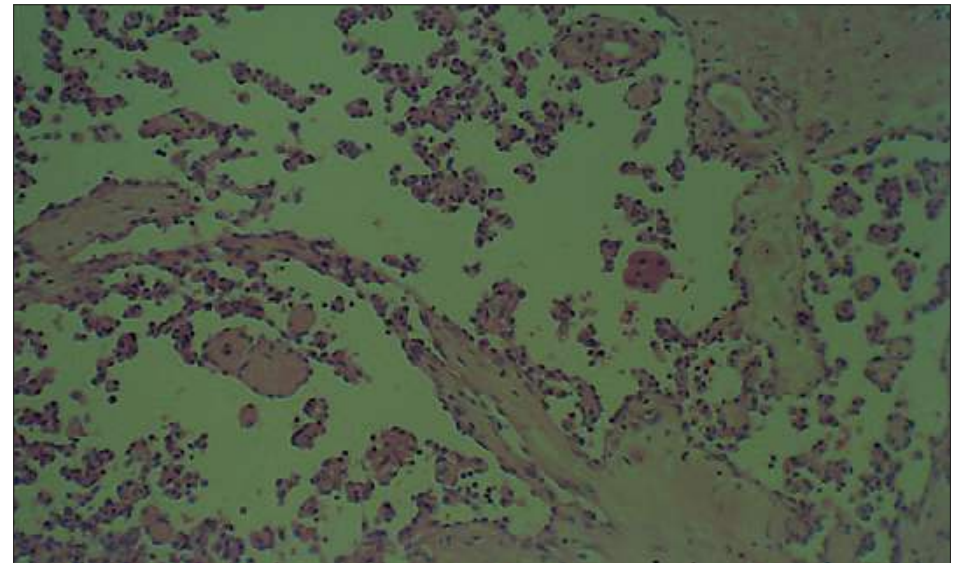
Figure 14/ *Large, empty space containing papillary fronds of angiosarcoma, few red cells and a single clump of liver cells in the right middle part of the field.*
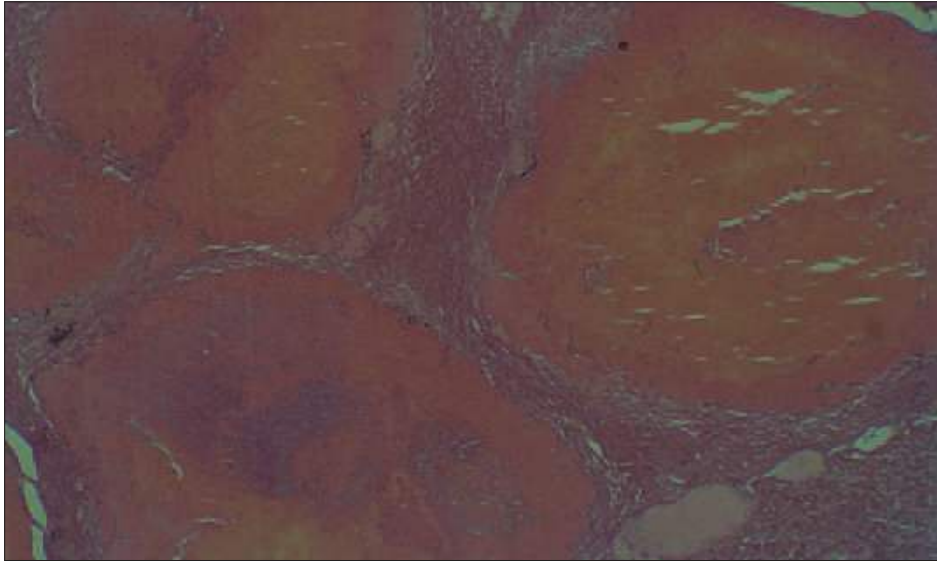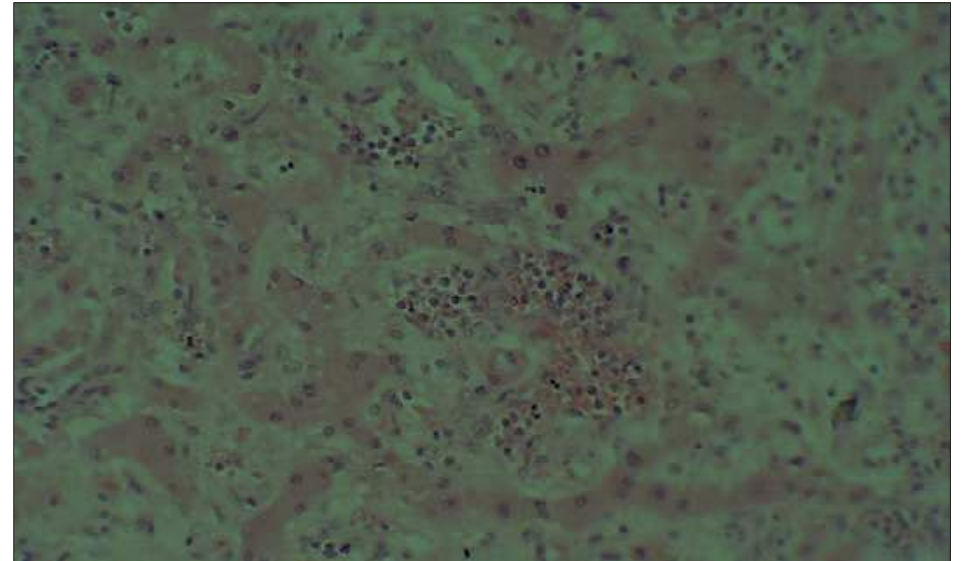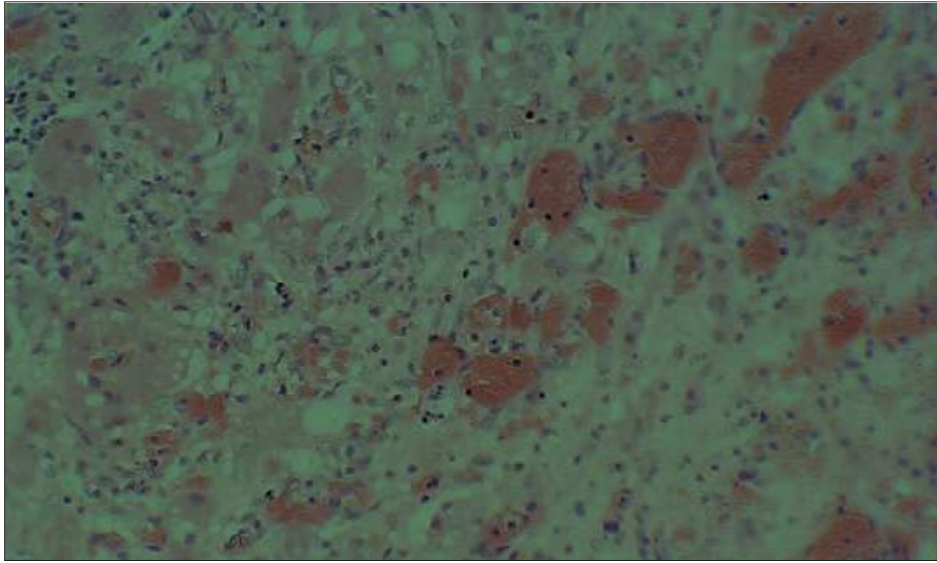
Figure 15/ Large blood-filled spaces resembling peliosis.

Figure 16/ Diffusely scarred area with few tumour cells.

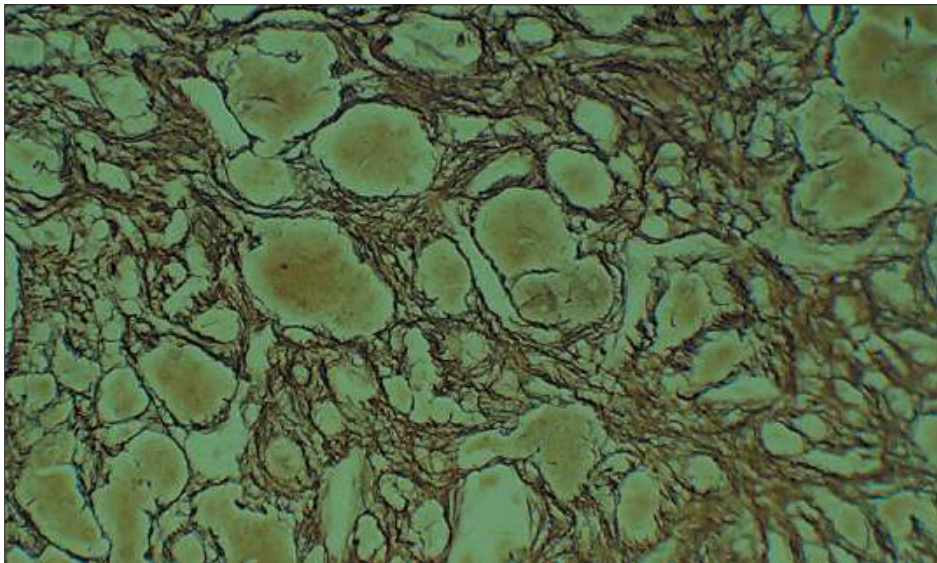*Figure 17/ Angiosarcoma with a solid, spindle cell pattern.*

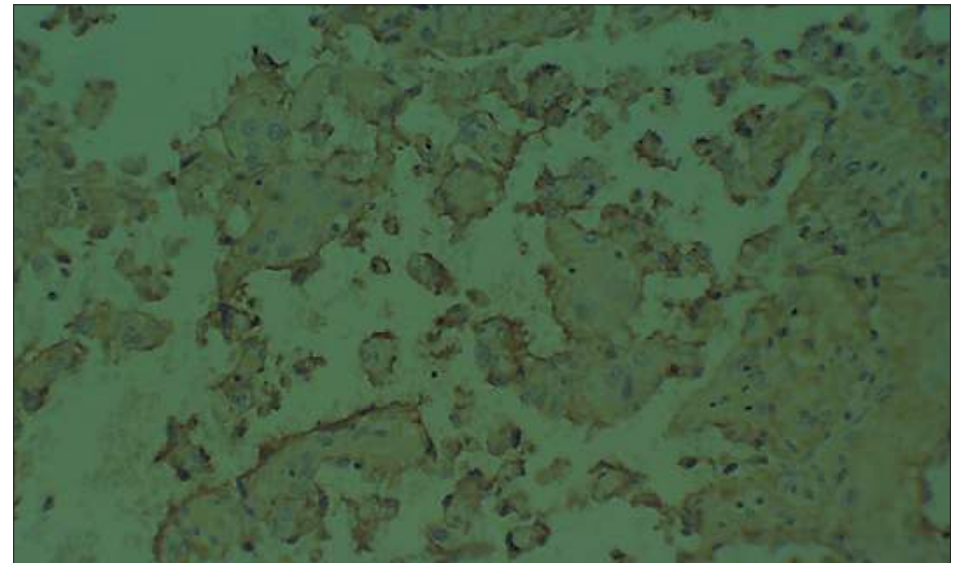*Figure 18/ Extramedullary haemopoiesis in angiosarcoma.*

Figure 19/ *Erythrophagocytosis in angiosarcoma.*
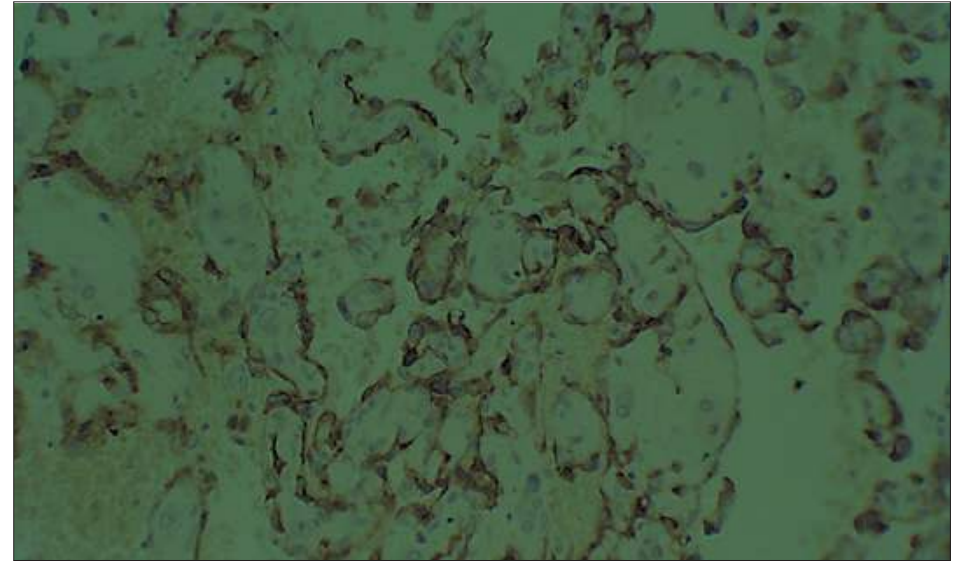
Figure 21/ *Papillary clumps of angiosarcoma react positively with antibody against CD31 or CD34 cluster antigens.*

Figure 20/ *Coarse reticulin fibers obliterate sinusoidal lumina.*

Figure 22/ *A similar positive result is shown by antibody against Factor VIII related antigen/von Willebrand factor.*