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Invited Review

Bacillary angiomatosis. A «new» disease with a broadening clinicopathologic spectrum

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Summary. Bacillary angiomatosis (BA) is a reactive vasoproliferative lesion occurring almost exclusively in immunocompromised individuals in response to infection by a bacillus closely related to *Rochalimaea quintana*. The commonest site of involvement is the skin, in the form of multiple erythematous nodules, but bacillary angiomatosis can also present in a wide variety of sites such as soft tissues, bone, lymph node, liver and spleen. Some patients may present with persistent fever and bacteraemia. Bacillary angiomatosis is characterized histologically by proliferation of blood vessels lined by plump endothelium, associated with an interstitial eosinophilic or amphophilic material formed by aggregated bacilli, best demonstrated by the Warthin-Starry stain. A heavy infiltrate of neutrophils is frequently, but not invariably, present. In the liver and spleen, there may be in addition features of peliosis. It is important to be able to diagnose bacillary angiomatosis correctly because prompt treatment with antibiotics is potentially life-saving.

Key words: Bacillary angiomatosis, Warthin-Starry stain, Acquired immunodeficiency syndrome, Vascular neoplasm

Historical aspects

In 1987, Cockerell et al. reported the occurrence of a new entity, epithelioid angiomatosis, in patients with the acquired immunodeficiency syndrome (AIDS). The patients developed solitary or multiple skin lesions, with or without involvement of the internal organs. The disease either resolved or proved lethal. Histologically, the lesions showed overlapping features of epithelioid (histiocytoid) haemangioma and pyogenic granuloma. This disease entity has evoked a lot of interest, and doubts have even been raised that it might merely represent a variant of Kaposi's sarcoma (Brooks and Fisher, 1987).

Inspired by an earlier report by Stoler et al. (1983) that bacilli could be demonstrated in an unusual subcutaneous vasoproliferative lesion in an AIDS patient, LeBoit et al. (1988) reported successful demonstration of numerous bacilli in the interstitium of «epithelioid angiomatosis» with Warthin-Starry stain, thus providing proof that this lesion had an infective aetiology and was not a neoplasm. The bacilli were thought to be identical to those causing cat-scratch disease (CSD), and this entity was renamed «bacillary angiomatosis» (BA) (Angritt et al., 1988; Cockerell and Friedman-Kien, 1988; LeBoit et al., 1989). Recent molecular DNA analysis, however, has shown that the bacillary agent is a Rickettsia-like organism closely related to *Rochalimaea quintana*, distinct from the CSD bacillus (Relman et al., 1990). It should be noted that most cases reported in the literature as «CSD» in patients with AIDS represent examples of BA.

Recently, bacillary peliosis of the liver and spleen is recognized to be another morphological manifestation of BA (Perkocha et al., 1990; Alkan and Orenstein, 1991; Humberson, 1991; Relman et al., 1991a).

Clinical features

BA occurs almost exclusively in patients with AIDS and individuals immunocompromised for reasons other than AIDS (such as transplant recipients on immunosuppressive therapy), but it has also been reported to occur in an immunocompetent individual (Cockerell et al., 1990; Cockerell and LeBoit, 1990; Kemper et al., 1990; LeBoit, 1990). In the latter circumstance, the cutaneous lesions are limited to the site of inoculation of the bacillary agent.

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BA most commonly occurs in the skin and mucosae (such as oral, conjunctival, anal and gastrointestinal). The purple-red or skin-coloured cutaneous and mucosal lesions may be solitary or generalized (up to thousands), ranging from pinpoint papules to large polypoid tumors which may be ulcerated. Clinically they may be indistinguishable from pyogenic granuloma and Kaposi's sarcoma. There can be in addition or exclusive involvement of a wide variety of sites, such as deep soft tissue, bone, lymph node, spleen, marrow, liver, lung and possibly brain (LeBoit, 1990; Milam et al., 1990; Schinella and Greco, 1990). Visceral involvement may result in lymphadenopathy, hepatosplenomegaly, derangement of liver function and osteolytic lesions, often associated with fever and systemic upset. Less commonly, the patients present with a syndrome of fever and bacteraemia with no obvious mass lesions (Slater et al., 1990; Relman et al., 1991a).

BA shows excellent response to erythromycin, but other antibiotics such as trimethroprim-sulfamethoxazole, tetracycline, doxycycline, isoniazid and rifampicin have also been reported to be effective (Koehler et al., 1988; LeBoit et al., 1988; Axiotis et al., 1989; Cockerell and LeBoit, 1990; Slater et al., 1990). The lesions resolve completely after treatment, although they can sometimes recur after cessation of therapy (LeBoit et al., 1988; Axiotis et al., 1989; Cockerell and LeBoit, 1990).

Pathology

Gross Pathology

The appearance of the skin lesions ranges from superficial polypoid nodules to deep dermal-subcutaneous rounded masses. Lymph node involvement may result in an appearance simulating lymphoma or metastatic cancer, in which small nodules are scattered in the parenchyma, or the entire lymph node may be converted into a tan-coloured fleshy mass. Splenic involvement is characterized by multiple, sometimes coalescing, fleshy nodules with bulging cut surfaces scattered in the parenchyma; liver involvement also tends to be multinodular. The nodules of BA are tan to light brown in colour, punctuated by reddish spots representing foci of ectatic vascular spaces or interstitial hemorrhage. Splenic and hepatic bacillary peliosis, characterized by multiple blood-filled spaces measuring up to several millimetres, is occasionally found (Perkocha et al., 1990; Alkan and Orenstein, 1991).

Microscopical Features

In this section, the general features are discussed first, followed by the specific features in the various tissues.

Regardless of the site of involvement, the basic histological architecture of BA is lobular proliferation of blood vessels (Fig. 1), although morphological variations on this basic theme may be wide. The lobules are composed of proliferated endothelium-lined blood vessels, which are usually of capillary size (Fig. 2). However, the vessels can be dilated, congested, irregularly-shaped or branched (Fig. 3). Occasionally the lesion appears solid, with the individual vascular lumina being barely discernible (Fig. 4), but reticulin stain will reveal the rounded contours of the individual unicellular or multicellular vasoformative units. There may be extravasation of red blood cells. The protuberant endothelial cells are cuboidal, polygonal or hob-nailed, and possess a moderate amount of granular, pale to clear, often finely vacuolated, cytoplasm with indistinct borders (Figs. 2, 4). There may be central or eccentric cytoplasmic vacuoles containing occasional red cells, indicative of early vascular differentiation (Fig. 4). The nuclei are oval to elongated with occasional indentations, and contain fine, dust-like chromatin with several small nucleoli. There is usually only mild nuclear atypia and infrequent mitosis, but endothelial cells exhibiting enlarged, pleomorphic nuclei and frequent mitoses are occasionally seen (Fig. 5). Rarely, irregular, branched vascular spaces lined by

Fig. 1. BA involving lymph node showing coalescent lobules of vascular proliferation. H&E, × 45

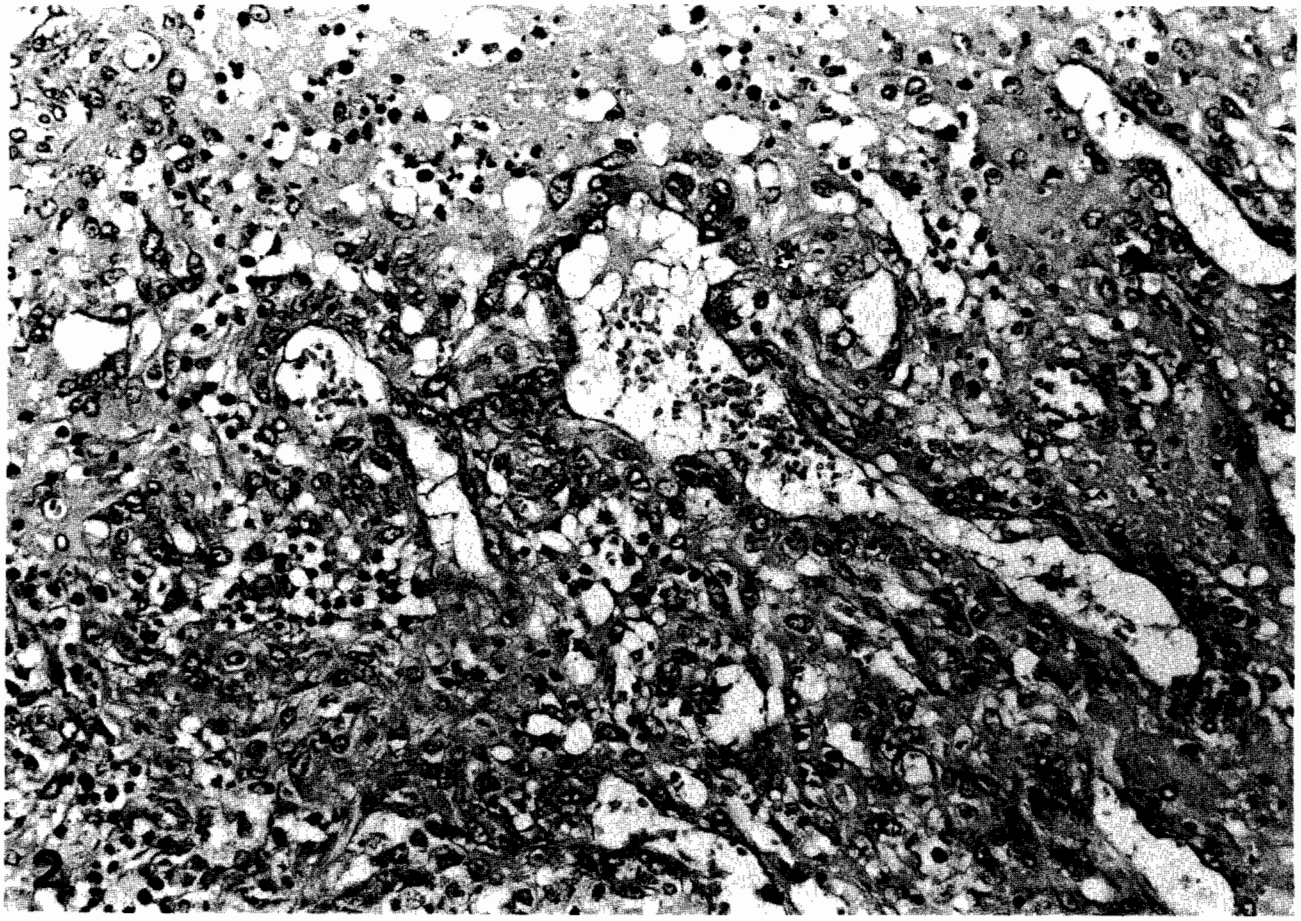

Fig. 2. BA showing typical triad of capillary proliferation, leucocytoclasis, and granular interstitial materials. H&E, × 300

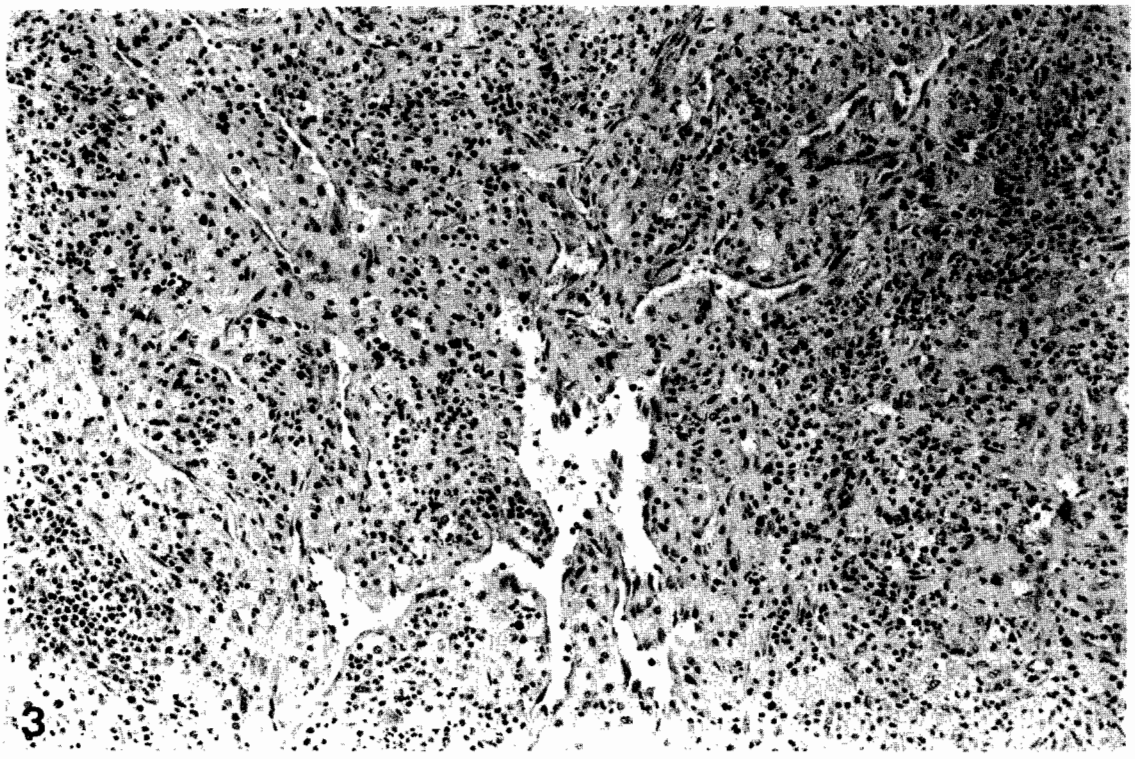

Fig. 3. Irregular branching vascular channels with numerous neutrophils in the background. H&E, × 120

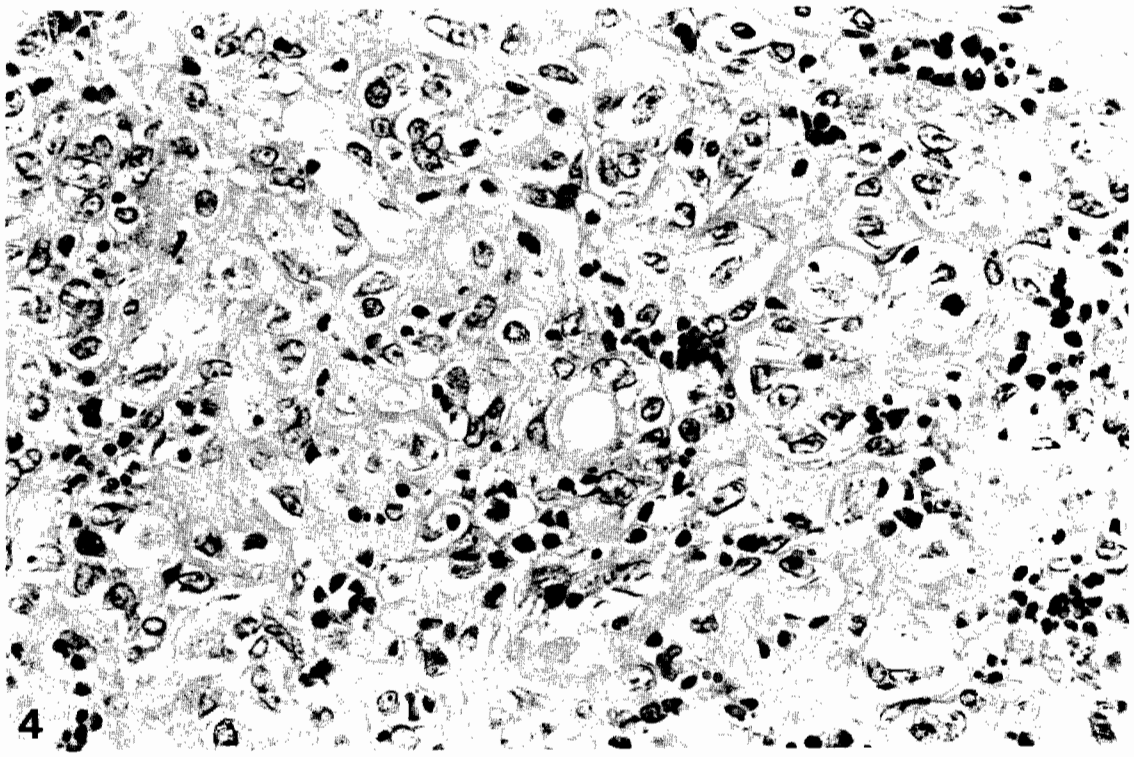

Fig. 4. More solid area featuring closely packed vessels with barely discernible lumina. Some cells are vacuolated. Note the interstitial granular materials. H&E, × 400

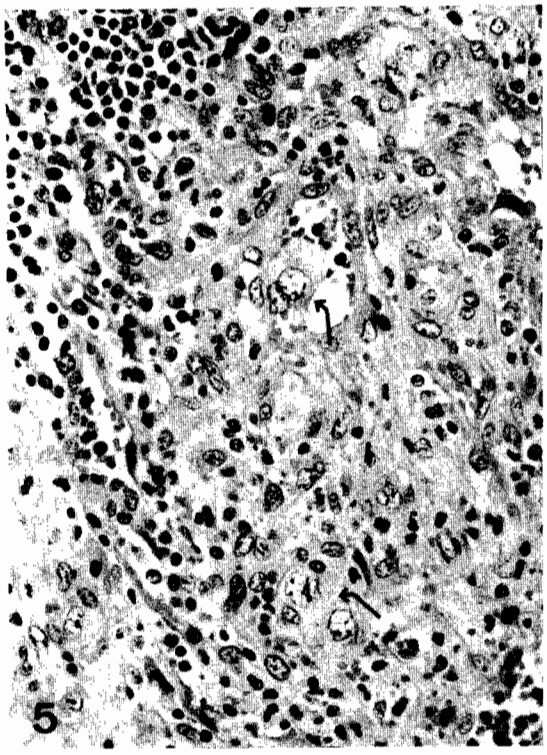

Fig. 5. Occasional atypical endothelial cells with large, bizarre nuclei (arrows). H&E, × 180

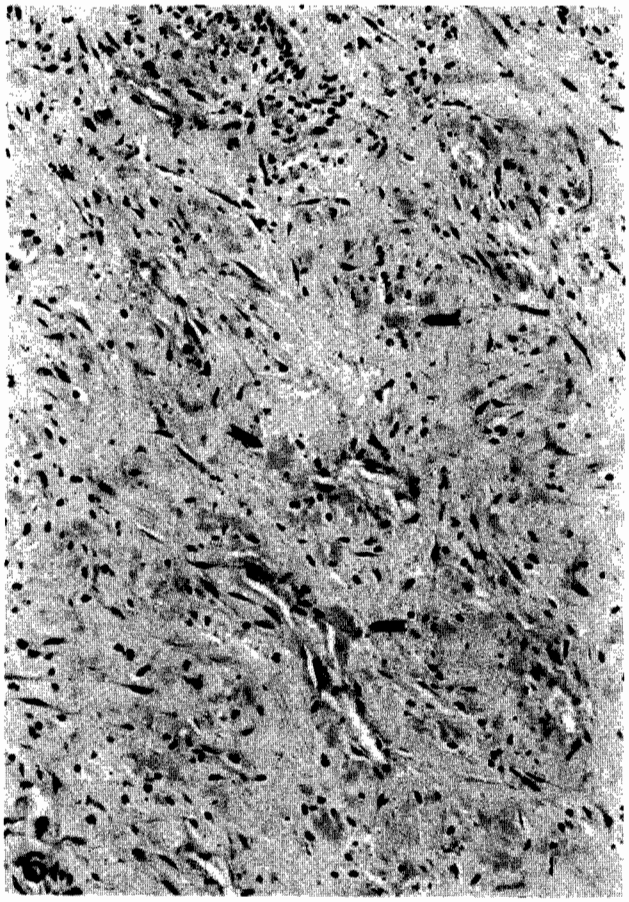

Fig. 6. Hepatic BA, with spindled endothelial cells forming narrow, cleft-like lumina. Note the granular interstitial deposits (arrows). H&E, × 150

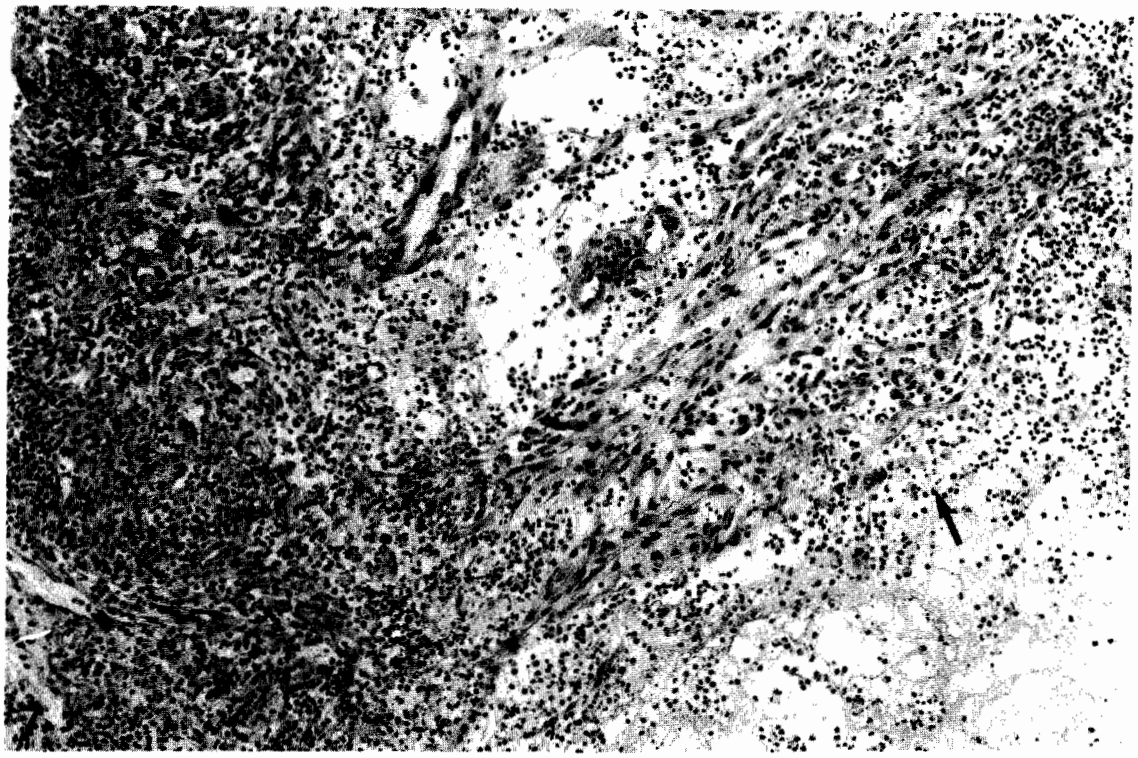

Fig. 7. BA with loculated oedema, spindle cell proliferation, foamy cells (arrow), and numerous polymorphs in the background. H&E, × 100

flat to plump endothelial cells may dominate, mimicking angiosarcoma (Figs. 3, 6). Sometimes, isolated polygonal or plump spindled cells, probably endothelial in nature, are found in the stroma (Figs. 6, 7). Rarely, the spindle cells may form short curved fascicles, reminiscent of Kaposi's sarcoma (Fig. 8). The endothelial nature of the plump cells lining the vascular channels as well as the polygonal/spindled cells in the interstitium is confirmed by positive immunostaining for factor VIII-related antigen and *Ulex europeaus* agglutinin, and ultrastructural demonstration of Weibel-Palade bodies (Cockerell et al., 1987; Axiotis et al., 1989; LeBoit et al., 1989).

BA is further characterized by the presence of a homogeneous, granular, or fibrillary amphophilic to eosinophilic interstitial material, and neutrophilic infiltration with prominent leukocytoclasis (Figs. 2, 4, 6). The interstitial material is formed by dense clumps of extracellular, entangled bacilli, as revealed by Warthin-Starry stain (Fig. 9). Gram's, Ziehl-Neelsen or Giemsa staining is negative. The bacilli can also be visualized in semithin sections stained with toluidine blue (LeBoit et al., 1988; Walford et al., 1990). Electron microscopy shows that the bacilli possess trilaminar cell wall and electron-dense granular material; some are arranged in chains and some may show branching. The number of bacilli varies from case to case and within different parts of the same lesion. The bacilli are usually closely associated with neutrophil aggregates, and are often more prominent in the more cellular areas of vascular proliferation. The number of neutrophils is also highly variable; neutrophils can be so abundant that there is abscess

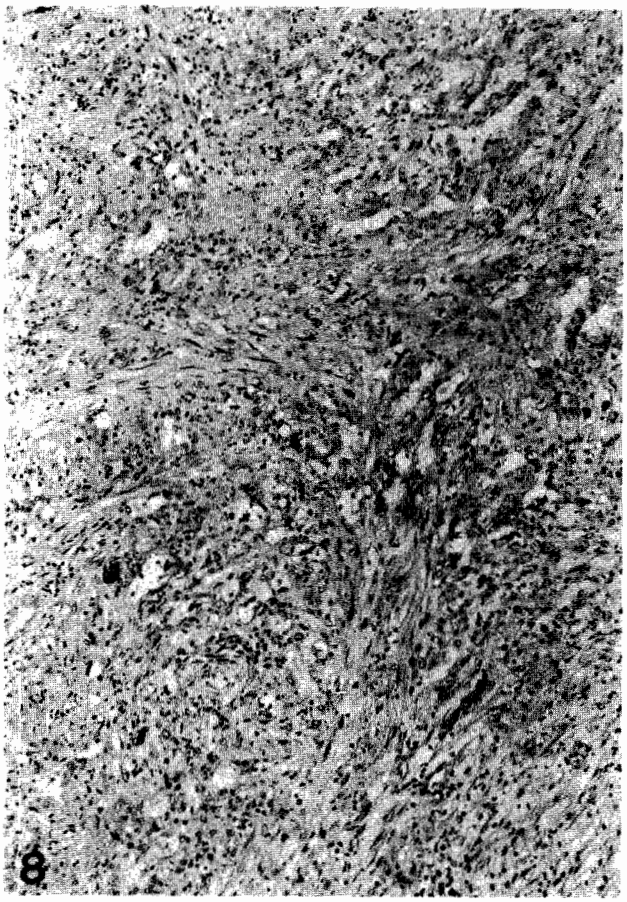

Fig. 8. Curved criss-crossing spindle-cell fascicles mimicking those of Kaposi's sarcoma are occasionally found. H&E, × 75

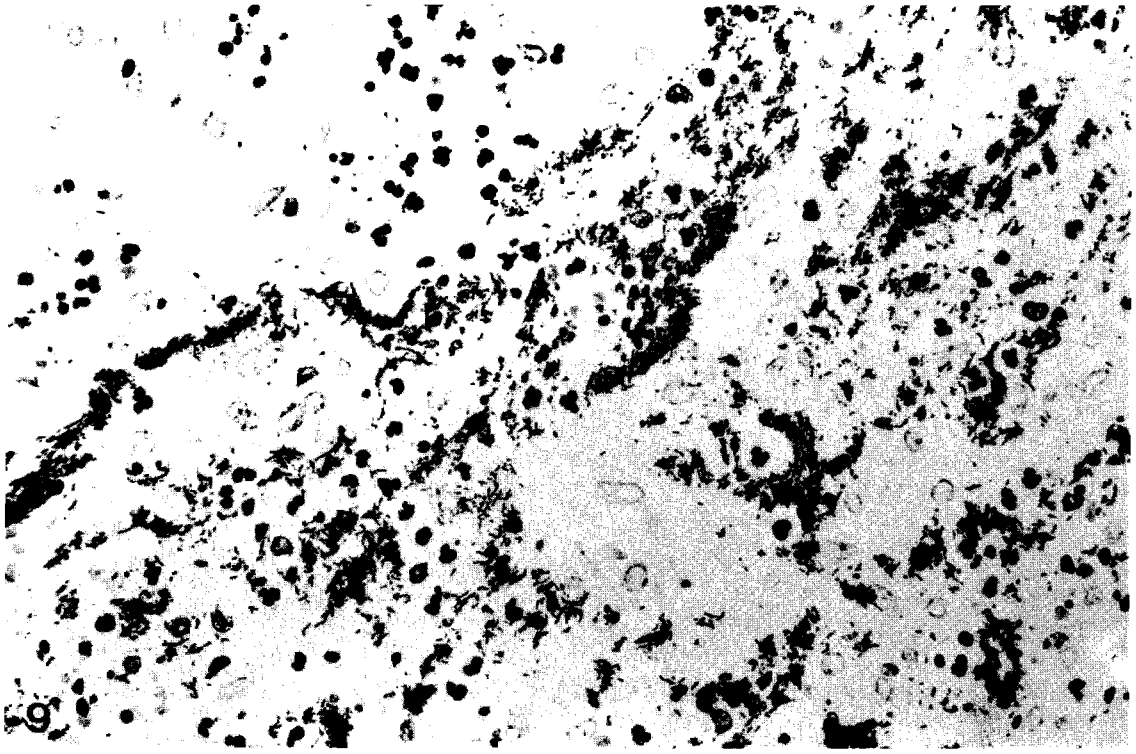

Fig. 9. The granular interstitial materials are revealed to be clumps of entangled bacilli by the Warthin-Starry stain. Warthin-Starry, × 400

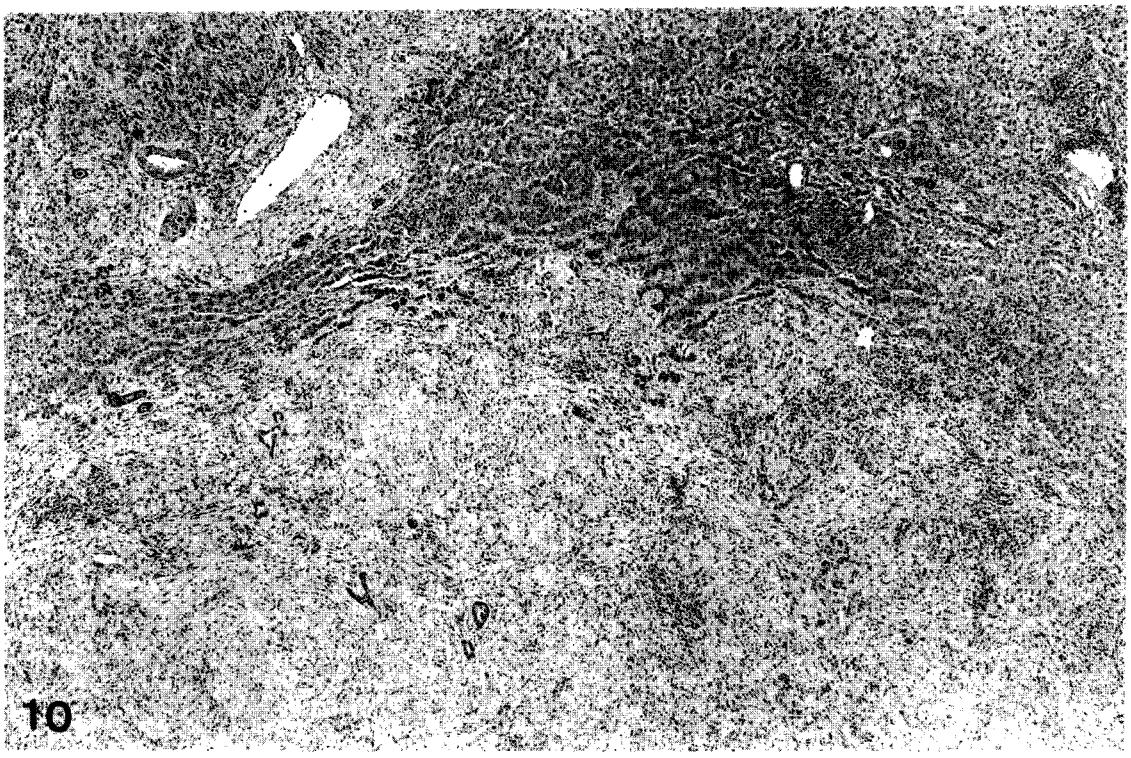

Fig. 10. Hepatic BA, with markedly enlarged portal areas containing widely separated bile ductules. H&E, × 40

Fig. 11. Large, blood-filled cystic cavity (peliosis) surrounded by proliferated vessels. H&E, × 75

formation (Fig. 7), but they can be remarkably sparse, particularly in lymph nodes (Fig. 4) (Chan et al., 1991).

In addition to the triad of vascular proliferation, interstitial bacillary deposition and neutrophilic infiltration, other features may be observed in individual cases. The stroma of BA is variably fibrotic, myxoid or oedematous, but occasionally there may be loculated pools of oedema fluid, in which bacilli are concentrated at the rims of the locules (Fig. 7). Coagulative necrosis and collections of foamy histiocytes may also be found (Fig. 7). A case of pulmonary BA was reported to show profuse collections of epithelioid histiocytes (Humberson, 1991).

In the skin, the low power pattern of BA shows a striking resemblance to pyogenic granuloma (lobular capillary haemangioma) by virtue of the polypoid lobular vascular proliferation and epithelial collarette formation (Knobler et al., 1988; LeBoit et al., 1988, 1989; Cockerell and LeBoit, 1990; Jiménez-Acosta et al., 1990; Walford et al., 1990). The surface may be ulcerated. The superficial lesions frequently appear loose and oedematous, while the more deeply located ones are more solid (Fig. 4). Within each vascular lobule, more mature ectatic vessels are often located centrally, while the vessels appear more immature and solid in the peripheral areas (Cockerell and LeBoit, 1990).

Lymph node involvement is characterized by coalesing nodules of proliferated vessels in the cortical and paracortical areas (Fig. 1). Granulomas similar to those found in CSD have also been described in nodal BA (Humberson, 1991; Perkocha et al., 1991). The uninvolved parenchyma can show follicular hyperplasia, plasmacytosis, or sinus histiocytosis (Angritt, 1988; Chan et al., 1991).

In the liver, BA expands the portal areas with entrapment of portal vessels and bile ductules, and also forms discrete nodules of variable sizes (Fig. 10). However, the proliferating vessels can also insinuate along the sinusoids, closely mimicking the growth pattern of an angiosarcoma. Another peculiar occurrence is peliosis, in which irregular blood lakes are found (Fig. 11). The blood lakes are, however, rimmed by fibromyoxid tissue containing inflammatory cells, dilated capillaries and clumps of granular purple material composed of bacilli (Fig. 6) (Perkocha et al., 1990). Similar peliotic lesions can also occur in the spleen. It has been postulated that peliosis develops in the liver and spleen but not in other sites as a result of different responses of the local endothelial cells in these sites to the same stimulus (Perkocha et al., 1990).

Differential diagnosis

It is most important to distinguish BA from Kaposi's sarcoma since both conditions commonly occur in the setting of AIDS (Berger et al., 1989). Although focally BA may be indistinguishable from Kaposi's sarcoma (including the presence of spindle cells), the circumscribed lobular growth of the former contrasts with the infiltrative margins of the latter. The vascular channels in Kaposi's sarcoma are frequently slit-like, while those in BA are usually more well-formed. Epithelioid endothelial cells, interstitial bacilli and neutrophil infiltration are not features of Kaposi's sarcoma. On the other hand, the PAS-positive hyaline globules characteristic of Kaposi's sarcoma are absent in BA.

Pyogenic granuloma (lobular capillary haemangioma) closely mimics the superficial cutaneous lesions of BA histologically, especially in ulcerated lesions, wherein there are polymorph infiltration and fibrin deposition that resembles the granular bacterial clumps of BA. However, fibrin deposition and neutrophils in pyogenic granuloma are limited to the superficial ulcerated portion, whereas interstitial deposition of bacilli in BA is more abundant in the deep, solid part of the vascular lobules. Leucocytoclasis (disintegration of neutrophils with formation of nuclear dust) is often prominent in BA, but is rare in pyogenic granuloma. In pyogenic granuloma, the endothelial cells are usually flat or

plump-spindled rather than epithelioid, and there is a prominent component of pericytes, which is not a feature of BA (LeBoit et al., 1989). Admittedly, the distinction may be very difficult by histological evaluation alone. In fact, some laboratories in AIDS-prevalent regions perform Warthin-Starry stain on every case carrying a presumptive diagnosis of pyogenic granuloma.

Epithelioid haemangioma is a benign vascular tumor characterized histologically by proliferation of small vessels lined by plump endothelium, usually accompanied by a rich infiltrate of eosinophils and lymphocytes. Epithelioid haemangioendothelioma is a vascular neoplasm of borderline malignancy characterized by cord-like growth of vacuolated plump endothelial cells within a hyalinized or cartilage-like stroma. Both vascular neoplasms are distinctive for the proliferation of epithelioid (histiocytoid) endothelial cells with dense, hyaline eosinophilic cytoplasm due to abundance of intermediate filaments, whereas the cytoplasm of the endothelial cells in BA is pale and finely vacuolated (due to paucity of intermediate filaments) (LeBoit et al., 1989). In contrast to epithelioid haemangioma, BA does not show a propensity to involve the luminal lining and media of muscular vessels (Chan et al., 1989). Furthermore, interstitial deposition of bacilli and infiltration of neutrophils are not features of epithelioid haemangioma and epithelioid haemangioendothelioma (Chan et al., 1988; Enzinger and Weiss, 1988).

BA can be distinguished from angiosarcoma by the absence of destructive infiltrative growth, bizarre anastomosing maze-like vascular lumina, prominent endothelial tufting and significant nuclear pleomorphism, and most important of all, the presence of bacilli in the interstitium (Enzinger and Weiss, 1988; Tsang et al., 1991). However, in isolated fields, these two conditions can be indistinguishable (Schinella and Greco, 1990). Prominence of neutrophils and interstitial eosinophilic material in a tumour suspected to be an angiosarcoma should lead to careful exclusion of BA.

Bacillary peliosis is distinguised from its non-infective counterpart (peliosis hepatis or splenic peliosis) by the presence of an inflammatory fibromyxoid stroma containing bacterial clumps around the blood-filled peliotic spaces (Perkocha et al., 1990).

Pathogenesis

The causative agent of BA was previously thought to be the CSD bacillus, because 1) the staining properties and morphology of the bacilli were identical to those of CSD bacilli, 2) ultrastructural features of the BA bacilli (trilaminar cell wall) were identical to those of CSD bacilli, 3) the bacilli of BA were immunoreactive with an anti-serum raised against the CSD bacilli, and 4) some patients with BA gave a history of scratch by a cat (Hall et al., 1988; Koehler et al., 1988; Tuur et al., 1988; Marasco et al., 1989; Kemper et al., 1990; Milam et al., 1990; Relman et al., 1991b). However, a number of features are not typical of CSD. First, CSD is characterized by suppurative granulomas with inconspicuous vascular proliferation, bearing little resemblance to the histological features of BA. Second, BA is highly responsive to erythromycin treatment, whereas CSD is not. Third, the fatty acid compositions of the bacilli of BA and CSD as demonstrated by gas liquid chromatography are different (Cockerell et al., 1991).

Interestingly, the histological features of BA are strikingly similar to those of verruga peruana (Carrion's disease), a cutaneous lesion resulting from infection by *Bartonella bacilliformis*, which is endemic in certain parts of South America (Arias-Stella et al., 1986). The minor differences are the presence of phagocytosis of bacilli by endothelial cells and lack of a conspicuous interstitial material in verruga peruana. An angiogenic factor distinct from other known eukaryotic angiogenic factors has recently been isolated from *B. bacilliformis*; it stimulates human endothelial cells to proliferate and to release tissue plasminogen activator (García et al., 1990). The latter is implicated in the degradation of basement membrane components and activation of collagenases, facilitating migration of endothelial cells towards the angiogenic stimuli. Taking such an analogy, angiogenic factors released by the BA organism may be responsible for the vascular proliferation in BA.

Recently, employing an ingenious method, Relman et al. (1990) were able to sequence the DNA of the BA organism. They employed the polymerase chain reaction to amplify the 16S eubacteria-specific ribosomal gene fragments directly from tissue samples of BA. All cells contain multiple copies of a gene encoding a 16S small subunit of ribosomal RNA, in which hypervariable sequences are interspersed with conserved sequences (Eisenstein, 1990; Relman et al., 1990). Therefore an unknown eubacterium can be identified from a tissue sample through amplification techniques using primers that anneal to flanking sequences conserved within the kingdom of eubacteria. Further analysis of the variable portions of the amplified DNA can provide valuable information on the phylogenetic relations with other organisms. It was concluded that the BA agent is previously uncharacterized, and is most closely related to *Rochalimaea quintana*, a pathogenic rickettsia. Since this fastidious organism has recently been successfully cultured, more information will be forthcoming concerning its natural habitat, mode of transmission, other properties and its full clinicopathological spectrum (Slater et al., 1990; Relman et al., 1991a).

The current evidence strongly supports the role of the *R. quintana*-like organism in the pathogenesis of BA (Relman et al., 1991a). However, it is unclear whether viruses play an additional permissive role, as evidenced by the presence of cytomegalovirus inclusions

in one case (Abrams and Farhood, 1989) and the demonstration of Epstein-Barr virus DNA in the nuclei of the endothelial cells by *in-situ* hybridization in two cases (Guarner and Unger, 1990). The human immunodeficiency virus (HIV), the causative agent of AIDS, can also potentially play a role because a cytokine produced by HIV-infected cells has been demonstrated to stimulate vascular proliferation (Nahamura et al., 1988; Vogel et al., 1988).

Conclusion

Since BA is potentially life-threatening as a result of visceral/mucosal involvement and is yet highly responsive to antibiotic treatment, this is a diagnosis not to be missed. A high index of suspicion is required, particularly in immunocompromised individuals - the Warthin-Starry stain should be performed whenever BA is a diagnostic possibility. Some laboratories may have problems with the Warthin-Starry stain, a fastidious stain which may be rendered uninterpretable as a result of non-specific deposits. An alternative method to demonstrate the bacilli is to re-embed the tissue in resin; the bacilli can be recognized in the toluidine blue-stained semi-thin (1 μm) section.

The pathologist's duty does not end on rendering a histological diagnosis of BA. Since the patients are often immunocompromised, the sections should be further scrutinized for other infective agents (such as cytomegalovirus, cryptococcus) and neoplasms (such as Kaposi's sarcoma, lymphoma) (Berger et al., 1989; Perkocha et al., 1991).

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