Tumoral, quasitumoral and pseudotumoral lesions of the superficial and somatic soft tissue: new entities and new variants of old entities recorded during the last 25 years. Part X: Excerpta VIII

Lesioni tumorali, quasitumorali e pseudotumorali delle parti molli somatiche e superficiali: entità nuove e varianti di entità già note, descritte negli ultimi 25 anni. Parte X: Excerpta VIII


Ectopic hamartomatous thymoma (EHT) is a rare benign soft tissue neoplasm which predominantly affects adult males and almost exclusively occurs in the supraclavicular, suprasternal or rarely in the presternal region. It was described almost simultaneously by Smith and McClure as an “unusual subcutaneous mixed tumor exhibiting adipose, fibroblastic and epithelial components”1 and Rosai and coworkers as a “spindle cell thymic anlage tumor”2. The term “ectopic hamartomatous thymoma” was coined by Rosai in 19843; since then, approximately 30 cases of EHT have been published, and, most recently, a large series encompassing 21 cases (including 16 newly identified examples from AFIP files) has appeared4. The tumor is highly distinctive clinicopathologically, but the controversy about its origin persists. It has been suggested that EHT may originate from the third and fourth branchial pouch, the cervical canal of His, salivary glands or the ultimo-branchial body5-8. A very recent proposal is to classify the lesion as a branchial anlage mixed tumor4.

CLINICAL FINDINGS
EHT demonstrates a strong predilection for the lower neck region. In particular, many tumors have been found in close proximity to the sternoclavicular joint. However, one case of EHT has been reported outside the typical location – the dorsal part of the chest9. There is a striking predilection for young males. In the AFIP series just cited, the male to female ratio was 20:1, and the median age was 40 years9. The preoperative duration of the lesions ranged from 2 months to 30 years. The lesion is benign. Local excision seems to be curative, but rare patients with recurrent disease have been documented. No metastases or tumor-related deaths are known.

PATHOLOGICAL FEATURES
The tumors are usually solitary, well-circumscribed, nodular or multilobular masses ranging in size from 2.0 to 19.0 cm in greatest dimension (mean size, 5.1 cm; median, 4.0 cm). They have a firm or rubbery consistency, with a mottled gray-white to tan cut surface, with scattered yellow foci. Microscopically, EHT is typically well marginated and composed of three components: 1. spindle cells (account for 20-95% of an entire lesion); 2. epithelial structures (constitute 5-35% of a lesion); and 3. mature adipose tissue (1-70%) (Fig. VIII-1i). Spindle cells are usually arranged in a fascicular, lattice-like pattern or storiform pattern or rarely in a palisade fashion resembling schwannomatous structures. They have regular, plump, oval to elongated, sometimes wavy nuclei with fine chromatin and indistinct nucleoli. The cytoplasm is pale or eosinophilic. These cells histolo-
ologically differ from stromal fibroblast-like cells, which possess smaller and darker nuclei, express vimentin and are negative for cytokeratins. Typically, the spindle cells merge almost imperceptibly with the epithelial component (Fig. VIII-1i). The appearance of the latter is variable; it may take the form of small islands, cysts (sometimes filled with flocculent material), anastomosing cords, branching strands or acinar structures (Figs. VIII-1ii → VII-1iv). The cysts can be large (up to 2 cm in greatest dimension). The most common type of epithelium is non-keratinizing stratified squamous. Other epithelial types described in EHT include keratinizing squamous, cuboidal, basa-
roid, oxyphilic, acinic, and ductal epithelium, with or without a myoepithelial layer. Mature fat is usually interposed haphazardly among the spindle cells and the epithelial component. Rare features reported include myoid differentiation, sarcomatoid changes within the spindle cell compo-
ent, clear cell change, large bizarre cells in the epithe-
lial component, psammomatous microcalcifications, patchy lymphocytic infiltrates, and the development of a carcinoma in EHT 4,10-14.

A recent comprehensive immunohistochemical analysis revealed a complex immunophenotype with a diver-
sive keratin profile 4. The spindle cells had a myoe-
 epithelial phenotype, as evidenced by the co-expression of keratins (5, 5/6, and 14), alpha-smooth muscle actin, CD34) by close intermixture of spindle cell and adipo-
se tissue components; however, it lacks the presence of the epithelial structures and is much less circumscri-
bled. Synovial sarcoma has nuclear atypia, which is not seen in EHT. Bronchogenic cysts and heterotopic sali-
vary gland tissue manifest only scarce epithelial struc-
tures, in contrast to EHT.

Differential diagnosis

The clinicopathological features of EHT are distincti-
ve, and if the pathologist is aware of the lesion, there should be no diagnostic problems. The histological dif-
ferential diagnosis of EHT includes myoepitheliomas and mixed tumors of skin adnexal or salivary gland ori-
gin (especially those with lipomatous metaplasia), biphasic synovial sarcoma, some peripheral nerve sheath tumors, dermotofibrosarcoma protuberans, bronchogenic cysts, heterotopic salivary gland tissue and cystic teratomata.

Myoepitheliomas and peripheral nerve sheath tumors are distinguished by S-100 positivity. EHT lack chond-
droid differentiation, which is frequently seen in beni-
g mixed tumors. Additionally, ductal structures in be-
nign mixed tumors usually have a less complicated ar-
chitecture than those in EHT. DFSP can bear some si-
mlarity to EHT (some cases of EHT can be reactive for CD34) by close intermixture of spindle cell and adipose tissue components; however, it lacks the presence of the epithelial structures and is much less circumscri-
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tures, in contrast to EHT.

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The topic of heterotopic (ectopic) meningotheelial tissues in the skin and subcutis is complex, which is even reflected in the hodgepodge of terminology that has been used to describe them. Here is an incomplete list of terms applied to these lesions: meningioma (including types I, II, III), rudimentary meningocele, acoelic meningeal hamartoma, sequestrated meningocele, hamartoma with ectopic meningotheelial elements, classic meningocele, and cutaneous heterotopic meningeal nodules. We believe that at present at least 3 entities can be delineated from a histogenetic and clinicopathological standpoint. These are: 1. meningioma, which is a true neoplasm of meningocytes; 2. meningocele, which represents a developmental malformation, i.e. herniation of the dura and the arachnoid through a congenital defect of the cranium or the vertebral; and 3. hamartoma with ectopic meningotheelial elements/rudimentary meningocele. Admittedly, despite almost identical clinicopathological features of hamartoma with ectopic meningotheelial elements (HEME) and rudimentary meningocele (RM), the controversy still exists as to whether the two are separate conditions or represent a single entity, and if so whether this is a hamartoma or a form of meningocele in which the underlying connection to the meningeal space became obliterated. Evidence supporting the existence of RM as such includes: 1. rare cases in which connections (albeit rudimentary) to the central nervous system (CNS) and minute osseous defects were identified; 2. cases with lesions located at sites that are thought to represent neural tube closure sites (the human neural tube multi-site closure model has recently been introduced in opposition to the traditionally held hypothesis according to which neural tube closure begins in the cervical region and proceeds from there in a continuous bidirectional way); and 3. rare cases in which HEME/RM were associated with other developmental anomalies.

**Clinical Findings**

Clinically, solitary nodules with a size of approximately 3 cm, located on the head, most commonly in the occipital area, are found in otherwise healthy persons. Rare cases have occurred overlying the cervical spine. The lesions are identified at birth or in early childhood. Hair is often absent in the affected area. The clinical impression is often that of a benign cystic, vascular malformation or meningocele.

**Pathological Features**

Histopathologically, HEME and RM are indistinguishable and manifest an admixture of collagenous mass, mature fat, irregular, anastomosing vessel-like spaces, scattered nerve bundles and irregular strands or small nests of meningotheelial cells (Figs. VIII-2i → VIII-2iv). Psammoma bodies and collagenous bodies are scarce. Prominent pseudovascular channels lined by meningotheelial cells may give a lesion the appearance of a vascular neoplasm. This impression is enhanced when plump, hyperchromatic and/or occasional multinucleated cells are seen alongside the vessel-like spaces. Focally, meningotheelial cells may merge with the pseudovascular channels or assume a solid pseudoinfiltrative growth pattern. Skin adnexa are absent within the collagenous mass.

**Immunohistochemistry**

Immunohistochemically, the meningotheelial cells stain for vimentin and epithelial membrane antigen (EMA) and show no reaction with CD34 and CD31.

**Differential Diagnosis**

Once the histopathological diagnosis has been established, the important clinical question is whether there is a connection to the CNS or not. The presence of a connection implies a possibility of infection complication (meningitis). As stated above, in the vast majority of cases there is no connection, not even a rudimentary one.

Because of the presence of numerous anastomosing, dissecting vessel-like channels in HEME/RM, the differential diagnosis includes various vascular neoplasms including angiosarcoma. The utilization of anti-endothelial markers enables a straightforward separation. Another entity to be considered in the differential diagnosis is giant cell fibroblastoma. Because of its microscopic pattern of relatively bland, stellate, polygonal and spindle cells interspersed between irregular pseudovascular spaces, giant cell fibroblastoma may be histopathologically confused with HEME/RM. Immunohistochemical evaluation is helpful in distinguishing between the two neoplasms; in contrast to meningotheelial elements, cells in giant cell fibroblastoma do not express EMA.

Meningioma is a neoplasm of the meninges of the brain or the spinal cord. It arises from a specialized cell type, the meningocytes. They are located in the arachnoid layer of the meninges, where they aggregate in clusters at the top of the arachnoid granulations and are known as arachnoid cap cells. The arachnoid granulations push against the dura mater and protrude into the venous sinuses. They are assumed to have the function of filters between blood and cerebrospinal fluid. The arachnoid granulations are distributed in relation to the nasofrontal sinuses, the cribiform plate, the temporal bone in proximity to the ear, and the spinal arachnoid. There are several ways by which meningioma can develop in the skin and superficial soft tissue. True primary cutaneous or subcutaneous meningiomas are thought to arise from nests of ectopic arachnoid cells that are misplaced during embryogenesis, or from arachnoid cell rests associated with cranial nerves. Clusters of arachnoid cells beyond the points of penetra-
tion of the dura by the cranial nerve have been identified in the third, seventh, ninth, tenth, eleventh and twelfth cranial nerves. Another possibility is an extension into the skin or subcutis from a meningioma of the CNS. It may result from a direct extension of a CNS tumor through the bone or herniation across a surgical or post-traumatic defect or from accidental implantation during a surgical intervention. Metastases of a cerebral meningioma in the soft tissue of the head and neck areas are exceedingly rare, which is explained by the absence of blood and lymphatic communications between the brain and head and neck soft tissues. Whatever the origin, cutaneous/soft tissue meningioma histopathologically appears as hypercellular lesions composed of variably sized lobules and nests of uniform oval to spindle meningothelial cells. The lobules often have a whorled configuration and are intermingled with fibrocollagenous tissue. Psammoma bodies and collagen bodies are usually numerous. Nuclear pleomorphism may be detected in aggressive tumors extending from the CNS.

Meningocele represents herniation of the dura and the arachnoid through a congenital defect of the cranium or the vertebrae. The term classical meningocele is often used for this condition. It usually presents itself at birth as a cystic transilluminable mass located along the most caudal segment of the spine, less often on the head. Associated congenital anomalies could be observed. Histopathologically, meningocele appears as a large cystic structure lined by pia-arachnoid cells. Meningothelial cells and psammoma bodies are sparse. The remnants of the dura mater are seen as coarse, eosinophilic collagenous fibers. A variably preserved stalk is found. Various reactive changes can be encountered.

Meningomyelocoele and meningoencephalocele are distinguished by the presence of neuroglial tissue from the CNS.

References

VIII-3. Neural lipofibromatous hamartoma

Lipofibromatous hamartoma of nerve is a neural non-neoplastic lesion composed of an overgrowth of epineurial adipose tissue, resulting in an expansion of the affected nerve trunk and – sometimes – of its branches. Several synonyms are used for referring to this condition, among which the most common are: intraneural lipoma, neural lipofibroma, neural fibrolipoma, neural fibrolipomatosis, neural lipomatous hamartoma, neural hamartoma, neural fibrolipomatous hamartoma, and fibrofatty proliferation of peripheral nerve.

The first description of this type of lesion has been credited by Silverman and Enzinger to Mason, the American orthopaedic surgeon who reported on two such cases in 1952-1953. Actually after careful review of the old literature it seems appropriate to credit this to other earlier authors: among them there are Bell & Inglis, even if similarly to Mason they failed to recognize the lesion as such at that time (as a matter of facts neuroma was the intraoperative diagnosis in all these cases). In 1964 this lesion was independently identified – although under different and still improper names – as a distinct entity by other orthopaedic surgeons. Subsequently, in 1969 Johnson & Bonfiglio first reviewed the literature of 13 cases published until then and added a case of their own, giving histological detail of the lesion and coining the term of lipofibromatous hamartoma of nerve, the most apt for describing this condition. Since then many papers appeared on this topic, mostly dealing with single case report or reporting on short series. The two largest series on this topic were published in 1985 and 1988, respectively, by Silverman & Enzinger, who reported on 26 cases, 25 of which involving the hands and one case involving the foot, and by Amadio et al., who described 18 cases, involving the hands in 14 and the feet in 4.

In some cases lipofibromatous hamartoma of nerve may be associated with digital soft tissue and skeletal enlargement (macrodactyly or megadactyly), a condition also known as macrodystrophia lipomatosa (Actually the original term of macrodystrophia lipomatosa was first introduced by Feriz in 1925 to designate...
the overgrowth of all the mesenchymal elements of an extremity, such as bones, muscles, nerves and vessels, with the main participation of fibroadipose tissue\(^{12}\). Its restriction to macrodactyly was due to Mikhail\(^{7}\) and Barsky\(^{13}\).

Seven cases in Silverman & Enzinger’s series\(^1\) and twelve cases in that of Amadio et al.\(^{11}\) were associated with macrodactyly, but the first examples of this more complex variant of disease are represented by case 1 of Mikhail\(^{7}\), and the cases of Jones\(^{14}\) and Baralidi and Ruiz\(^{15}\), the latter to be recorded as the first case ever described.

On a computerized based bibliography search (Medline, and Pubmed) until now nearly 175 cases have been found on record which were published subsequent to the first review of Bonfiglio and Johnson under the main terms of lipofibromatous or fibrolipomatous hamartoma of nerve and intraneural lipoma or fibrolipoma, of which about 125 affected the median nerve. Around one fourth of the same total (nearly 45 cases) were associated with a true macrodactyly (macrodystraphia lipomatosa) in the territory of the nerve distribution.

**CLINICAL FINDINGS**

Lipofibromatous hamartoma of nerve usually affects the median nerve, with the most common sites of presentation being the distal forearm and the hand in the wrist or palm. However, also the ulnar\(^{16,17}\), radial\(^{18-20}\), digital\(^{21,22}\), medial plantar\(^1\), peroneal\(^{25,27}\), and sciatic\(^28\) nerves can be involved. Rarely the lesion is bilateral with or without macrodactyly\(^{11,29-30}\); rarely it is situated proximally in a limb\(^31\). Exceptionally even cranial nerves can be affected\(^32\).

This type of lesion can be congenital or may occur later during life: children and young adults of both sexes up to their 4\(^{n}\) decade of life are mainly affected. Neural sensori-motor disturbances are the presenting symptoms, resulting in a classical tunnel carpal syndrome. Magnetic resonance imaging may be helpful for diagnosing this condition\(^28,33-35\), even though atypical findings may also be observed\(^33\). At surgery a rope-like or sausage-like nerve enlargement is found (Figs. VIII-3Ai, Figs. VIII-3Aii → VIII-3Bv). Perineural fibrosis as well as endoneural fibrosis may also be seen (Figs. VIII-3Aii → VIII-3iii, and VIII-3Biv → VIII-3Bv). Occasionally metastatic bone is found in the fibrofatty tissue\(^1,38-39\).

**DIFFERENTIAL DIAGNOSIS**

Clinically and surgically lipofibromatous hamartoma of nerve poses several diagnostic problems, partly depending on the possible presence of other associated physical signs. In cases without associated macrodactyly the differential diagnosis includes the following conditions: neural lipoma (both intra- and extra-neural type), neurinoma, traumatic neuroma, neural hemangioma, nerve sheath ganglion, plexiform neurofibroma, intraneural perineuroma (also called localized hypertrophic mononeuritis\(^40\)), hyperperipheral polineuropathy of Dejerine-Sottas (HSMN-III). In cases associated with true macrodactyly or pseudo-macro-dactyly, the differential diagnosis is clinically more complex, since true macrodactyly and pseudomacro-dactyly without lipofibromatous hamartoma may appear both as an isolated congenital anomaly (congenital partial gigantism without lipofibromatous hamartoma) and as part of a syndrome (neurofibromatosis type-1; Ollier’s disease; Maffucci’s syndrome; Klippel-Trenaunay-Weber syndrome; congenital lymphedema). Histologically intra-neural lipoma\(^{41,42}\) is the only differential diagnostic consideration versus lipofibromatous hamartoma of nerve: however, intraneural lipoma is well-encapsulated and resectable due to the presence of a plane of cleavage with the nerve fascicles and is devoid of the characteristic scattering of nerve fascicles in the fatty mass.

**BIOLOGICAL BEHAVIOUR**

Fibrolipomatous hamartoma of nerve is a benign condition. Neurolysis (nerve fasciotomy) with sparing of the nerve is the treatment of choice, accompanied by section of the transversal carpal ligament for decompression when the lesion – as is often the case – is located in the wrist. Since complete excision of the fibrofatty hamartoma would produce dramatic loss of neurological functions\(^7,40\), a fascicular nerve biopsy

**PATHOLOGICAL FEATURES**

Since lipofibromatous hamartoma of nerve is practically inextirpable, a fascicular nerve biopsy is the standard surgical specimen for pathological examination (Fig. VIII-3Aii: inset) at least in cases without macrodactyly. However few examples of bulbous-like surgically resected nerve are well documented in the literature\(^7,40\). Resection of the enlarged nerve is accomplished more often in cases of macrodystrophia lipomatosa, when the digital amputation has been planned for cosmetic purpose (Fig. VIII-3Bii). Grossly the affected nerve is dramatically enlarged up to several times the normal diameter. Histologically a fibrofatty expansion of the epineurial space is documented with primary and secondary nerve fascicles scattered in abundant adipose tissue (Fig. VIII-3-Aiii, Figs. VIII-3-Biii → VIII-3-Bv). Perineurial fibrosis as well as endoneurial fibrosis may also be seen (Figs. VIII-3-Aii → VIII-3-iii, and VIII-3-Biv → VIII-3-Bv). Occasionally metastatic bone is found in the fibrofatty tissue\(^1,38-39\).

**BIOLOGICAL BEHAVIOUR**

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Bibliography

CLINICAL FINDINGS

Ischemic fasciitis (IF) is a distinctive pseudosarcomatous fibroblastic proliferation. IF occurs in immobilized patients as a result of prolonged pressure and impaired circulation or in patients afflicted with melorheostosis. It is usually localized over bony prominences subjected to intermittent pressure, where it forms a poorly circumscribed, painless soft tissue mass 1 to 8 cm in diameter. It was, however, described in vulva in a paraplegic patient as well. It is mainly located in the subcutis and sometimes extends into the muscle tissue and dermis. Most patients are elderly, with a peak incidence between the seventh and ninth decades. Females are affected slightly more often than males.

PATHOLOGICAL FEATURES

Histologically IF is composed of multinodular zones of fibrinoid necrosis, fibrosis, myxoid changes, and areas of vascular proliferation, involving the adipose tissue (Fig. VIII-4i). Necrosis has a characteristic appearance, consisting of central zone of liquefactive and coagulative necrosis, having sharp uneven borders, and staining deeply red to violet with H&E. Artificial sequestration can place the necrosis into the peripheral parts of sequestered tissue (Fig. VIII-4ii). Foci of necrosis are frequently surrounded by a fringe or palisade of capillary proliferation and fibroblasts. Muscular vessels often reveal deposits of fibrin within the muscle wall or around the vessels (Fig. VIII-4iii) with fibrin thrombi in various stages of recanalization. A small amount of secondary acute inflammatory cells and extravasated erythrocytes are also observed. Evidence of primary vasculitis or myositis is, however, never seen. Some fibroblasts may be large and even bizarre, with abundant deep staining cytoplasm, large eccentric nuclei and a smudged, hyperchromatic nucleus with prominent nucleoli. These cells are reminiscent of the fibroblasts in proliferative fasciitis (Fig. VIII-4iv).

IMMUNOHISTOCHEMISTRY

Immunohistochemically the lesional cells are vimentin positive, and occasional fibroblastic cells are smooth muscle actin and CD68 positive, and all cells are S-100 protein and desmin negative. Enlarged, bizarre fibroblastic cells are CD34 positive.

GENETICS

Genetics is unknown in IF. The association of IF with another pseudosarcomatous process, namely bizarre parosteal osteochondromatous proliferation (Nora’s reaction) is of utmost interest, because a genetic aberration, a balanced translocation t(X;6), has recently been described in the latter condition.

BIOLOGICAL BEHAVIOR

Although the lesion can repeatedly locally recur, IF is a benign process, and the patients are cured by conservative excision. Local recurrence is usually secondary to persistence of predisposing cause (pressure ischemia).

DIFFERENTIAL DIAGNOSIS

IF should be distinguished from sarcomas on one side and from proliferative fasciitis on the other side. The location over bony prominences is not a feature of proliferative fasciitis/myositis, and the distinctive arrangement of IF into central zonal liquefactive and coagulative necrosis surrounded by a palisade of capillary proliferation and vessels with fibrinoid deposits slightly admixed with atypical fibroblastic cells is a feature not seen in either sarcomas nor proliferative fasciitis/myositis.

References

Nephrogenic fibrosing dermopathy (NFD) is a new disorder, first recognized in 1997, that occurs in patients with renal failure. More than 100 cases from 23 States in the USA and from Europe have been confirmed at the NFD Registry established at Yale University 1.

**Clinical Features.**
The affected patients usually have end-stage renal disease and characteristically develop indurated, ill-defined plaques localized to extremities and trunk. The lesions are often acute, symmetric, and painful and may be associated with some degree of functional disability. Epidemiologic data have yielded several distinct clinical patterns of disease onset 1.

**Pathological Findings**
Histological findings may vary depending on the stage of disease development. The typical features are thickening of collagen bundles, mucin deposition, and a scant septa of the subcutaneous fat can be seen 2.

Ultrastructurally, the lesional cells are oval and spindle-shaped and possess long thin cytoplasmic processes (dendrites), which are adjacent to, and sometimes encircled by elastic fibers and collagen bundles. In some areas, dendritic processes can be found within collagen bundles. The cells have prominent rough endoplasmic reticulum. Some elastic fibers appear to be coated by electron-dense material, which may represent calcification 2.

**Differential Diagnosis**
Differential diagnoses of NFD include classic scleromyxedema, scleroderma (generalized and localized) and a variety of scleroderma-like diseases (eosinophilic fasciitis, eosinophilia-myalgia syndrome, toxic oil syndrome). Clues to NFD include sparing of face, absence of paraproteinemia and systemic involvement, and absence, histologically, of pools of mucin and inflammatory cells 2.

Scleromyxedema is characterized by papular mucinosis associated with diffuse thickening of the skin. The face is often involved, which is usually not the case in NFD. Apart from skin involvement, some systemic manifestations such as dysphagia, proximal myopathy, inflammatory polyarthrits, hematological disorders and seizures can be encountered in scleromyxedema. IgG-λ paraproteinemia and IgG-κ paraproteinemia are found in approximately 80% and 13% of cases, respectively. Histopathologically, scleromyxedema manifests numerous stellate and bipolar fibroblasts scattered among thick, haphazardly arranged collagen bundles, increased dermal mucin, and infiltrates of lymphocytes and sometimes of plasma cells. Pools of mucin can accumulate, widely separating the collagen bundles 2.

Systemic sclerosis (generalized scleroderma) is characterized by a symmetrical tightening and induration of the skin, predominantly affects females in the age range 20-60 years and often has a slowly progressive course. It is typically associated with Raynaud’s phenomenon, circulating autoantibodies and internal organ involvement 2.

Patients with morphea profunda (a localized form of scleroderma) present with thick, taut, bound-down skin. Histologically, no proliferation of spindle-shaped cells is seen in morphea profunda, while lymphocyte infiltrates, which are uncommon in NFD, are typical 2. Eosinophilic fasciitis (Shulman’s syndrome), another differential diagnosis of NFD, is typified by diffuse fasciitis, hypergammaglobulinemia and eosinophilia. Affected persons present with swelling, stiffness, and pain in the distal extremeties, often associated with malaise, weakness or fever. Polycyonal hypergammaglobulinemia and peripheral eosinophilia are seen in over 75% of the patients. The predilection sites are the extremities, but the trunk and face can be involved. Pitting edema or a peau d’orange dimpling or cobblestoning of the skin surface is found. Microscopically, there is fascial inflammation, edema, thickening and sclerosis of collagen bundles that commonly alternate with entrapped fat in parallel layers. The inflammatory infiltrate consists of lymphocytes, plasma cells, histiocytes, and sometimes eosinophils, and may extend into the fibrous septa of the subcutaneous fat. Dermal sclerosis is common 2.

**Biologic Behavior.**
The disease appears to run a chronic and unremitting course in most patients.
Bacillary epithelioid angiomatosis (BA) is a tumor-like vasoproliferative lesion caused by *Bartonella henselae* and *B. quintana* 12, occurring almost exclusively in immunocompromised hosts 1. Although cutaneous papulonodular lesions are the commonest manifestation, other locations including soft tissue 4, lymph node 5, liver, spleen and bone 6 have been described.

**CLINICAL FINDINGS**

The majority of BA present in males in the setting of AIDS, but is still an uncommon condition 3. The cutaneous lesions present clinically as multiple reddish papules and nodules that may resemble pyogenic granuloma. Involvement of mucosal sites (e.g. gastrointestinal and respiratory tracts) may result in hemorrhage. Splenic involvement can cause pancytopenia and cerebral lesions may lead to neurological complications 3.

**PATHOLOGICAL FEATURES**

The classic histopathologic feature of BA consists of a lobular proliferation of capillaries lined by plump epithelioid, protuberant endothelial cells (Figs. VIII-6i → VIII-6ii). The endothelial cells have clear cytoplasm and show mild atypia with occasional mitotic figures. An important clue to the diagnosis is the presence of clusters of fragmented neutrophils associated with collections of an eosinophilic granular or faintly basophilic extracellular material. The latter represent myriads of organisms that can be easily demonstrated with the Warthin-Starry silver stain (Fig. VIII-6iii). Occasionally BA may not display the above classic features with the vascular structures being obscure or resembling granulation tissue. Clearly, if the clinical impression is that of BA, then special stains are warranted to detect the organisms. In the liver, large peliotic blood-filled spaces are induced, whilst areas of fibrosis occur in splenic lesions. Both lesions harbor clusters of bacilli.

**SPECIAL STAINS AND ELECTRON MICROSCOPY**

Once a diagnosis of BA is entertained, the presence of organisms should be verified with the Warthin-Starry, Dieterle or Steiner stains: all of which will stain the bacilli. Other confirmatory methods include electron microscopy, immunohistochemistry, culture, and polymerase chain reaction. On electron microscopy, the organisms appear as bacillary forms with a trilaminar cell wall (Fig. VIII-6iv).

**BIOLOGICAL BEHAVIOR**

BA is still an uncommon condition. Even pathologists who practice in communities with immunosuppressed patients do not encounter BA frequently. BA responds to antibiotic therapy and hence distinction from neoplasia is critical. It has been proposed that prophylaxis for mycobacterial infection in HIV-infected patients may be decreasing the incidence of BA 3.

**DIFFERENTIAL DIAGNOSIS**

The differential diagnosis of cutaneous BA includes pyogenic granuloma (lobular capillary hemangiomia), angiolymphoid hyperplasia with eosinophilia (epithelioid hemangioma), verruga peruana, Kaposi’s sarcoma, and the epithelioid variant of angiosarcoma. Pyogenic granuloma is characterized by lobules of vascular tissue with central (often) ectatic vessels with branching lumens; neither of which is present in BA. Neutrophils in pyogenic granuloma are usually present beneath an ulcerated surface, whilst in BA they are associated with colonies of bacteria deep within the lesion. Angiolymphoid hyperplasia with eosinophilia features prominent epithelioid endothelial-lined vessels with eosinophilia. Neutrophils are not a feature of angiolymphoid hyperplasia with eosinophilia and eosinophils are rare in BA. Although verruga peruana shares many features with BA, lymphocytes and neutrophils are numerous in verruga peruana and neutrophils less abundant than in BA. In addition, the Rocha-Lima bodies of verruga peruana are intracellular clumps of organisms, whilst the bacilli of BA are extracellular. The tumor or nodular form of Kaposi’s sarcoma may occasionally present difficulties in the differential diagnosis of BA. Kaposi’s sarcoma comprises predominantly spindle cells and the eosinophilic globules representing residua of erythrocytes with a variable size are present in cells. Additionally, lymphocytes and plasma cells form the main inflammatory component in Kaposi’s sarcoma. Epithelioid angiosarcoma (cutaneous or deep soft tissue) is characterized by marked cytologic atypia of the eosinophilic epithelioid cells with prominent nucleoli, which mirror its highly aggressive behavior.
References

VIII-1. Ectopic hamartomatous thymoma

Fig. VIII-1. Ectopic hamartomatous thymoma: an admixture of spindle cells, epithelial structures and mature fat.

Fig. VIII-1i. Regular, plump, oval to elongated, spindle cells merging almost imperceptibly with the epithelial component that shows clear-cell change.

Fig. VIII-1ii. A morula-like, syringomatoid structure.

Fig. VIII-1iii. Acinar structures.

Fig. VIII-1iv. A psammoma body in a vessel-like space, which also contains meningothelial cells.

VIII-2. Hamartoma of the scalp with ectopic meningothelial elements/rudimentary meningocele

Fig. VIII-2. Hamartoma with ectopic meningothelial elements: an admixture of collagenous mass, mature fat, and irregular, anastomosing vessel-like spaces (arrow).
TUMORAL, QUASITUMORAL AND PSEUDOTUMORAL LESIONS OF SOFT TISSUE

Fig. VIII-2iii. Irregular, anastomosing vessel-like spaces lined by meningothelial cells.

Fig. VIII-2iv. A small island of meningothelial cells.

Fig. VIII-3Ai. Intraoperational finding in a 41-year old female patient with symptoms of tunnel carpal syndrome (detail in ref. 36). A rope-like lesion on the volar aspect of her left wrist is evident. Inset: a fascicular nerve biopsy from the same case.

Fig. VIII-3Aii. The nerve fascicles are embedded and dispersed in abundant adipose tissue. Perineurial fibrosis and endoneurial fibrosis are also coexistent.

Fig. VIII-3Aiii. Higher magnification of the previous figure.

Fig. VIII-3Bi. Megadactyly of the 2nd toe in a case of a 5-year old female affected by congenital macrodystrophia lipomatosa. Clinical view of the lesion. X-ray examination showed skeletal enlargement. A cicatrical scar is visible on the dorsum of the megadigit due to previous surgical attempt of partial reduction plastic.

VIII-3. Neural lipofibromatous hamartoma
Fig. VIII-3Bii. Transverse sections of the hypertrophic digital nerve, which was sent after amputation of the megadigit. Inset, for size comparison: cross section of a normal humeral nerve from an adult patient operated on of scapulo-humeral disarticulation.

Fig. VIII-3Biii. Microscopic image of the marked fibrofatty infiltration of the epineurial space.

VIII-4. Ischemic fasciitis (Atypical decubital fibroplasia).

Fig. VIII-4i. Ischemic fasciitis is composed of multinodular zones of fibrosis, myxoid changes and areas of vascular proliferation.

Fig. VIII-4ii. Artificial sequestration can place the necrosis into the peripheral parts of sequestered tissue.

Fig. VIII-4iii. Muscular vessels often reveal deposits of fibrin within the muscle wall or around the vessels.

Fig. VIII-4iv. Some fibroblasts are large and even bizarre, with abundant deep staining cytoplasm, large eccentric nuclei, smudged, hyperchromatic nucleus with prominent nucleoli. These cells resemble fibroblasts in proliferative fasciitis.
VIII-5. Nephrogenic fibrosing dermopathy

Fig. VIII-5i. Marked thickening of the dermis that gradually replaces the subcutis. The patient was a 51-year-old man who twice underwent kidney transplantation because of chronic renal failure due to chronic glomerulonephritis. Clinically, the lesion was a rapidly growing, indurated mass on his abdomen, which reached the size of 22x16 cm within 4 months.

Fig. VIII-5ii. A whole mounted section: thick, sclerotic dermis and reduction of the adipose tissue (from the same patient).

Fig. VIII-5iii. Sclerotic collagen bundles with scattered spindled cells (from the same patient).

Fig. VIII-5iv. Replacement of the subcutis by sclerotic collagen bundles. Scattered inflammatory cells are usually not the feature of NFD, but otherwise the patient manifested typical clinico-pathological features (from the same patient).

VIII-6. Bacillary epithelioid angiomatosis

Fig. VIII-6i. Bacillary angiomatosis. Low power of a skin nodule, close to the epidermis, bounded by an epithelial collarette, and thus resembling granuloma pyogenicum.

Fig. VIII-6ii. The features of the lesion consist of proliferating capillaries with foci of large cells with prominent nuclei.
Fig. VIII-6iii. Extracellular bacilli on the Warthin-Starry stain.

Fig. VIII-6iv. Electron micrograph of the bacteria.