Actas Dermosifiliogr. 2010;**101(3)**:201-216

ACTAS
Dermo-Sifiliográficas

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REVIEW ARTICLE

Histopathology of the More Common Viral Skin Infections

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Manuscript received July 18, 2009; accepted for publication July 28, 2009

KEYWORDS
Histopathology;
Viral infections;
Skin;
Herpesvirus;
Cytomegalovirus;
Papillomavirus;
Parapoxvirus

Abstract

We describe the histopathological characteristics of viral skin infections. Herpes simplex virus and varicella-zoster virus produce an intraepidermal vesicle with variable degrees of epithelial necrosis. Typical findings include keratinocytes with ballooned nuclei with a ground-glass appearance and giant multinucleated keratinocytes. In the endothelial cells of the dermal blood vessels, cytomegalovirus produces large eosinophilic nuclear inclusions surrounded by a clear halo. Human herpes virus 8 is etiologically associated with Kaposi sarcoma. In its early stages, this tumor contains blood vessels with a fine endothelium passing through the dermal collagen bundles. In the plaque and nodular stages, the vessel lumens are more clearly visible and there is a progressive increase in the number of neoplastic spindle cells with a low degree of pleomorphism and atypia, and occasional mitoses. The infiltrate is made up of lymphocytes and plasma cells. Contagious ecthyma and milker's nodule give rise to an acanthotic epidermis with ballooned keratinocytes containing eosinophilic cytoplasmic viral inclusions. Molluscum contagiosum shows lobules of epithelium that open onto the epidermal surface and characteristic inclusion bodies. Acanthosis, papillomatosis, and hyperkeratosis are observed in common warts, with confluence of the epidermal ridges in the center of the lesion and koilocytes.

PALABRAS CLAVE
Histopatología;
Infecciones víricas;
Piel;
Herpes virus;
Citomegalovirus;
Papilomavirus;
Parapoxvirus

Histopatología de las infecciones víricas cutáneas más frecuentes

Resumen

En este trabajo describimos las características histopatológicas de las infecciones víricas cutáneas. El herpes simple y el virus varicela-zóster producen una vesícula intraepidérmica con grados variables de necrosis epitelial. Son característicos los queratinocitos con núcleos balonizados con aspecto de vidrio esmerilado y los queratinocitos gigantes multinucleados. El citomegalovirus produce grandes inclusiones nucleares eosinófilas rodeadas de un halo claro en los endotelios de los vasos dérmicos. El herpes virus tipo 8 se relaciona etiológicamente con el sarcoma de Kaposi, que en sus fases iniciales muestra luces vasculares de endotelios finos disecando los haces de colágeno dérmicos. En las fases en placa y

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nodular las luces vasculares son más visibles, aumenta progresivamente el número de células fusiformes tumorales con discreto grado de atipia y pleomorfismo y algunas mitosis. El infiltrado se compone de linfocitos y células plasmáticas. El orf y el nódulo de los ordeñadores inducen una epidermis acantósica con queratinocitos balonizados que contienen inclusiones víricas citoplasmáticas eosinófilas. El molusco contagioso muestra lóbulos de epitelio abiertos a la superficie epidérmica con característicos cuerpos de inclusión. En las verrugas vulgares aparece acantosis, papilomatosis e hiperqueratosis, con confluencia de las crestas epidérmicas hacia el centro de la lesión y coilocitos.

Table 1 lists the most common viral skin infections, whose histopathologic features will be reviewed here.

Histopathologic Features of Skin Infections Due to Herpes Simplex Virus and Varicella-Zoster Virus

Histopathologic findings of biopsies of fully developed labial (Figure 1) and genital (Figure 2) vesicles due to herpes simplex virus, and vesicles caused by varicella virus (Figure 3) consist of an intraepidermal blister with varying degrees of epithelial necrosis. The most typical changes in the nuclei of epidermal keratinocytes involve the peripheral margination of chromatin, which seems to attach to the nuclear membrane. The resulting ballooned nuclei appear ringed and acquire a ground-glass appearance. The earliest noteworthy abnormality in the cytoplasm of these keratinocytes is the presence of vacuolization. Initially changes are found along the basal layer of the epidermis, but they soon spread upward until the entire thickness of the epidermis becomes affected.[1] Two mechanisms are

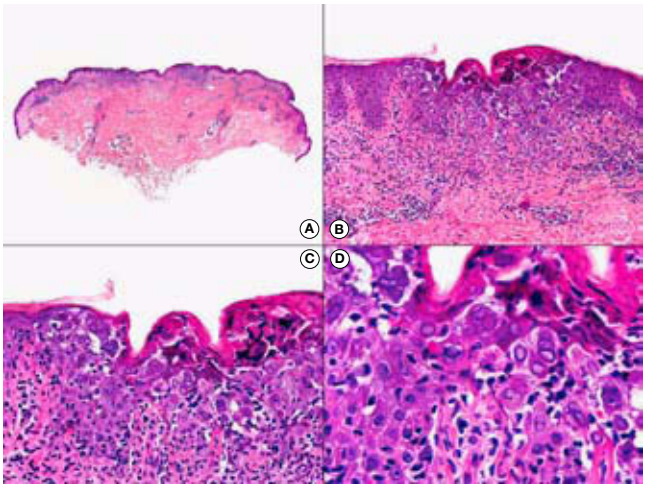

Figure 1 Histopathology showing a labial herpes simplex viral lesion that consisted of an intraepidermal vesicle with varying degrees of epithelial necrosis. The most typical changes are evident in the nuclei of epidermal keratinocytes, where there is peripheral margination of chromatin attached to the nuclear membrane. The result is keratinocytes with ballooned nuclei that appear ringed and have a ground-glass appearance. The earliest noteworthy abnormality in the cytoplasm of these keratinocytes is the presence of vacuolization. (Hematoxylin-eosin stain; A, magnification ×10; B, ×40; C, ×200; D, ×400).

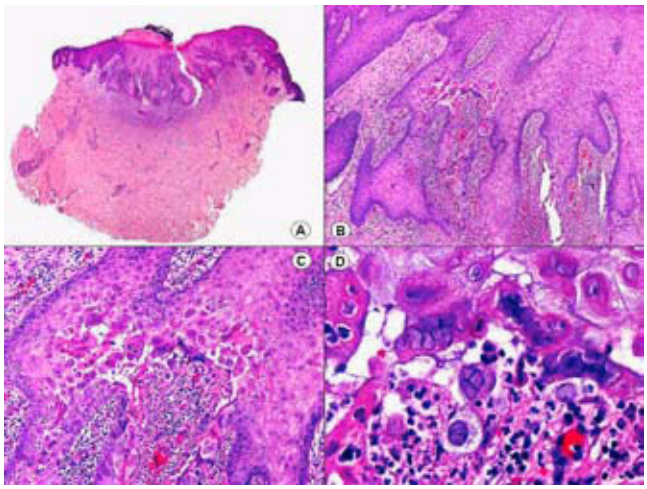

Figure 2 Histopathology showing a genital herpes simplex lesion with features similar to the preceding figure. (Hematoxylin-eosin stain; A, magnification ×10; B, ×40; C, ×200; D, ×400).

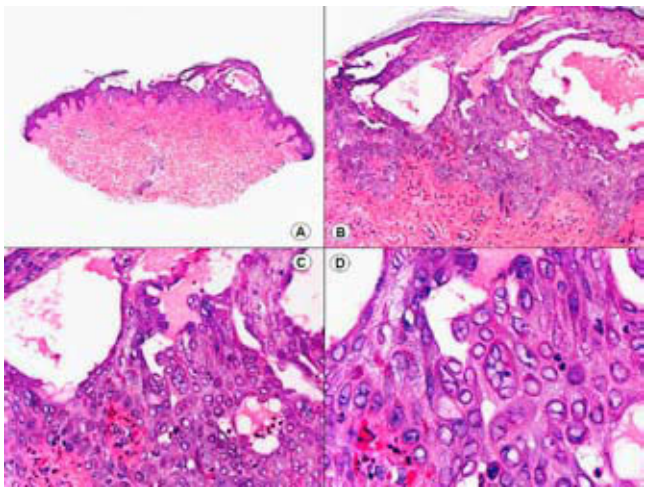

Figure 3 Histopathology showing a varicella lesion. The characteristics are indistinguishable from those found in labial or genital herpes simplex lesions. (Hematoxylin-eosin stain; A, magnification ×10; B, ×40; C, ×200; D, ×400).

Table 1 The Most Common Viral Skin Infections

Herpes virus
Herpes simplex types 1 and 2
Varicella and herpes zoster
Kaposi varicelliform eruption
Cytomegalovirus
Epstein-Barr virus
Human herpesvirus 6
Human herpesvirus 7
Human herpesvirus 8
Parapoxvirus
Contagious ecthyma (orf ulcer)
Milker's nodule
Molluscum contagiosum
Papillomavirus
Warts
Focal epithelial hyperplasia (Heck disease)
Bowenoid papulosis
Epidermodysplasia verruciformis
Parvovirus
Infectious erythema
Purpuric glove-and-sock syndrome
Coxsackievirus
Hand-foot-mouth disease

involved in the formation of intraepidermal vesicles: one is the ballooning of keratinocytes and the other is the reticular degeneration of the epidermis. It is common to see ballooned keratinocytes in viral infections. Affected cells appear swollen and isolated from neighboring cells because of the loss of intercellular connections. This process has been termed secondary acantholysis to differentiate it from the primary form, which appears in autoimmune diseases by way of antidesmosomal antibody mediation, as in variants of pemphigus. The cytoplasm of ballooned cells have an even, eosinophilic staining, and giant multinucleated cells are often present. These nuclei also display the aforementioned abnormalities, which can be observed in Tzanck cytodiagnostic smears.

Reticular degeneration is the result of swelling, or progressive hydropic degeneration, of epidermal keratinocytes, which appear large and clear, with traces of cytoplasm remaining at the periphery. As the cells swell, they break, contributing to the formation of intraepidermal vesicles. Unlike ballooning, reticular degeneration is not confined to viral infections, but can also be seen in acute contact dermatitis. Keratinocyte ballooning is generally more evident in cells at the base of a vesicle, whereas reticular degeneration is more intense on the vesicle surface and around the edges.

It is easier to see intranuclear eosinophilic inclusions in herpes lesion biopsies than in smears obtained by the Tzanck cytodiagnostic procedure. Inclusions are more evident in the nuclei of giant multinucleated cells, particularly if lesions are already several days old. In addition to the presence of isolated cells with the characteristic nuclear abnormalities, neutrophils and fibrin can also be detected inside herpes vesicles. Leukocytoclastic vasculitis in the superficial dermis underlying the lesion has been described in herpes simplex, varicella, and herpes zoster histopathology[2,3] (Figure 4). The dermal inflammation that typically accompanies these lesions is more marked in herpes simplex than in herpes zoster and it is not unusual to find atypical lymphocytes in herpes simplex infiltrates.[4] A recent study reported intense lymphocytic infiltrates giving the appearance of cutaneous lymphoma on histopathologic evaluation of skin infections due to either herpes simplex or varicella-zoster virus[5] (Figure 5, A and B). Immunohistochemical analysis of the infiltrate showed that it was composed mainly of T cells and that CD30 and CD56 expression was variable. Polymerase chain reaction (PCR) demonstrated monoclonal T-cell populations in 2 cases, increasing the difficulty of differential diagnosis with true lymphoma.

It is not unusual for herpes zoster lesions to affect epithelial cells of the pilosebaceous unit. The exclusive involvement of that unit, with subtle cytopathologic findings typically confined to the epithelium of the hair follicle and the sebaceous gland, without epidermal participation, has recently been proposed to be a specific sign of the onset of a herpes zoster lesion[6] (Figure 6). These subtle histopathologic findings indicate the so-called herpes incognito lesions, or herpetic folliculitis,[7] and they appear before vesicles develop. Epithelial cells of the outer root sheath and sebaceous cells are ballooned and their nuclei have a ground-glass appearance. They are multinucleated or mummified as a result of cellular necrosis secondary to varicella-zoster virus infection. Clinically, the onset is characterized by painful, erythematous papules. Several days pass before the vesicles typical of herpes zoster develop. More unusual is epithelial eccrine gland involvement, whether of the secretory portions or of the dermal or intraepidermal excretory ducts.[8] Cytologic characteristics cannot be identified in some tissue samples from herpes lesions of the adnexal epithelium, so that only serial slices can

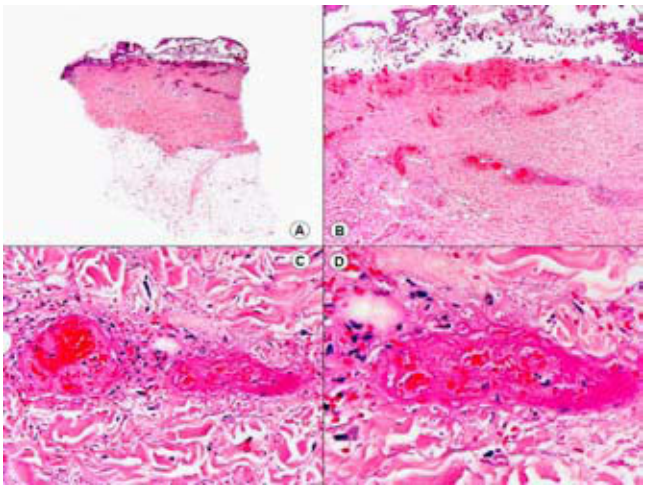

Figure 4 Histopathology of a herpes zoster lesion showing leukocytoclastic vasculitis in the dermis underlying the intraepidermal vesicle. (Hematoxylin-eosin stain; A, magnification ×10; B, ×40; C, ×200; D, ×400).

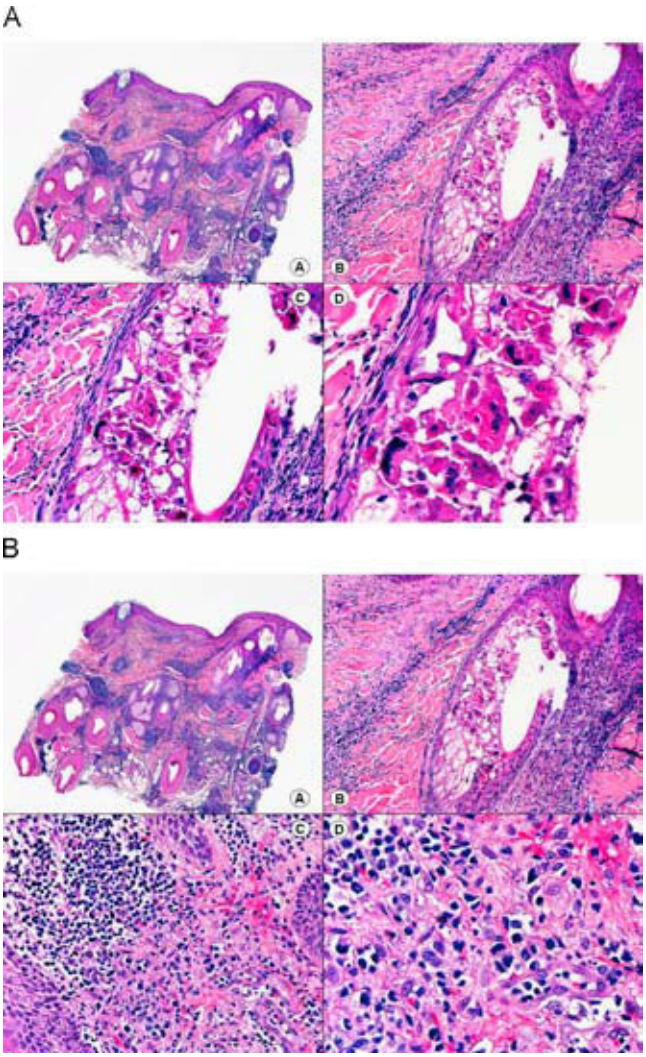

Figure 5 Histopathology of a pseudolymphoma overlying a herpes zoster lesion. A, the epithelium of a hair follicle and a sebaceous gland show cell changes typical of herpes virus infections. B, abundant atypical lymphocytes and evidence of mitosis in the infiltrate surrounding the lesion. (Hematoxylin-eosin stain; A, magnification ×10; B, ×40; C, ×200; D, ×400).

demonstrate the presence of giant multinucleated cells with a ground-glass appearance. Immunohistochemical analyses have also demonstrated viral antigen presence in nerve fibers of the dermis underlying herpes vesicles in varicella-zoster viral infections.[9,10]

The histopathologic differential diagnosis of herpes simplex and varicella-zoster viral infections may be established immunohistochemically. Commercial monoclonal antibodies are currently available for herpes simplex virus type 1 (Figure 7), type 2 (Figure 8), and varicella-zoster virus (Figure 9).[11,12] Immunohistochemical findings reveal diffuse staining of infected nuclei, although staining is more intense at the edges, confirming the observation of cells with peripheral margination of chromatin. However, these studies also demonstrate viral antigens not only in the epidermis but also in epithelial hair follicles and sebaceous glands, most often in varicella-zoster viral infections. These antigens are found in lower proportions in nerves and dermal structures. In contrast, herpes simplex viral antigens are usually located in epidermal keratinocytes and only occasionally affect the superficial portion of the follicular infundibulum and never the sebaceous glands or nerves of the dermis. Based on such immunohistochemical studies and the demonstration of viral antigens in various cutaneous structures, it has been possible to establish the sequence of herpes zoster lesion reactivation. In the initial phases, the varicella-zoster virus travels from the dorsal root ganglion to the sensory nerves of the

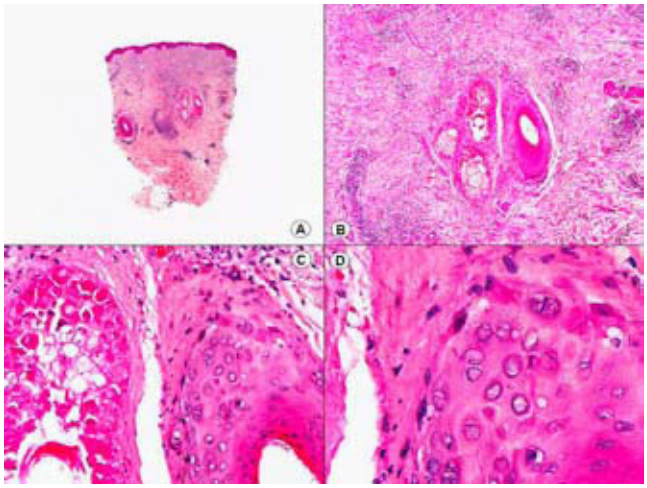

Figure 6 Views of a recently formed herpes zoster lesion showing typical epithelial cell abnormalities in hair follicles, without epidermal involvement. (Hematoxylin-eosin stain; A, magnification ×10; B, ×40; C, ×200; D, ×400).

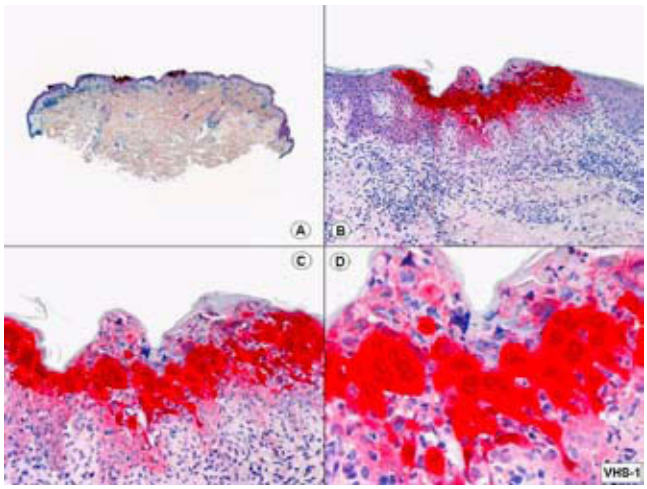

Figure 7 Immunohistochemical staining for herpes simplex virus type 1 of the lesion shown in Figure 1. (A, magnification ×10; B, ×40; C, ×200; D, ×400).

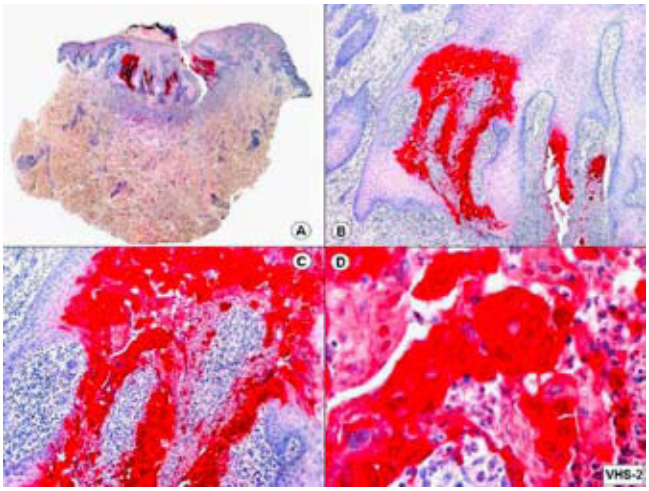

Figure 8 Immunohistochemical staining for herpes simplex virus type 2 of the lesion shown in Figure 2. (A, magnification ×10; B, x40; C, ×200; D, x400).

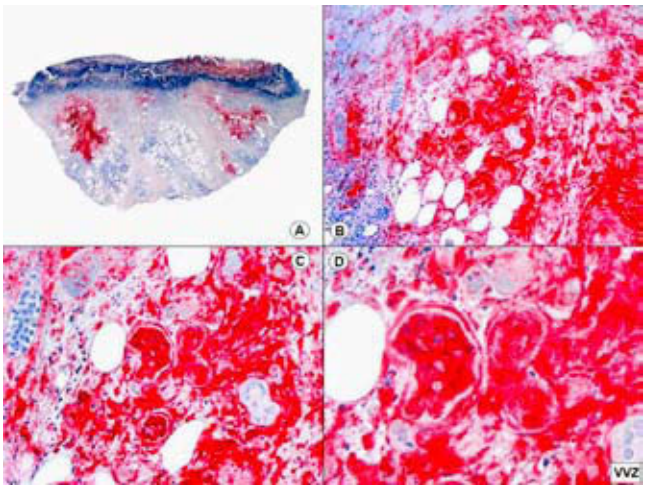

Figure 9 Immunohistochemical staining showing hair follicle and eccrine gland epithelial cell positivity for varicella-zoster virus in a herpes zoster lesion. (A, magnification ×10; B, ×40; C, ×200; D, ×400).

dermis and to perineural dendrocytes. (This is not the case in varicella lesions.) By means of these nerves, the virus reaches the pilosebaceous units, which are highly innervated and are the first epithelial structures infected. From the pilosebaceous unit the infection extends to epidermal keratinocytes. In other words, a histopathologic finding of pilosebaceous involvement is characteristic of incipient erythematous lesions, whereas epidermal involvement and the formation of vesicles will be found in fully developed lesions. The main cytopathologic findings inside varicella-zoster virus infected hair follicles are the keratinocytes of the outer root sheath of the isthmus and its connection with the sebaceous gland. These cells are much less evident in the epithelium of the infundibulum and the lower segment, apparently because the varicella-zoster virus has a tendency to migrate along myelinated sensory nerve fibers in the follicular isthmus. This virus has no predilection for nonmyelinated sensory nerve fibers innervating the epidermis.[6]

Many processes have been described as forming in scars left by herpes zoster lesions[13-51] (Table 2). These new lesions may appear immediately after resolution of the herpes zoster vesicles or some time later. The pathogenesis is poorly understood, although type II or IV hypersensitivity mechanisms and the Koebner phenomenon have been suggested as possible triggers. Results have been variable in studies attempting to demonstrate the presence of varicella-zoster viral material in lesions that form in scars. Discrepancies are probably attributable to variations in the interval between an acute episode and the appearance of secondary lesions after scarring; positive results are more likely in lesions that have formed recently than in those that develop over a longer period.

Histopathology of Cutaneous Infection Due to Cytomegalovirus

In cytomegalovirus infections the characteristic observations are made in endothelial cells of dermal blood vessels. The

Table 2 Lesions That Develop in Cutaneous Herpes Zoster Scars

Comedones[13]
Xanthomas[14]
Annular granuloma[15-28]
Sarcoid granuloma[16,29]
Tuberculoid granuloma[30]
Granulomatous vasculitis[16,31]
Unclassifiable granulomatous dermatitis[16]
Tinea[32]
Acneiform rash[33]
Furunculosis[34]
Contact dermatitis[34]
Nodular elastotic degeneration[35]
Pseudolymphoma[16]
Psoriasis[36]
Lichen planus[16,37,38]
Morphea[39,40]
Lichenoid graft-vs-host disease[41]
Eosinophilic dermatosis[42]
Reactive perforating collagenosis[43,44]
Lymphoma[45]
Leukemia[46]
Kaposi sarcoma[47]
Angiosarcoma[48]
Basal cell carcinoma[49]
Squamous cell carcinoma[49]
Cutaneous metastasis from internal carcinoma[50]
Sclerotic and atrophic lichen[16]
Rosai-Dorfman disease[16]
Granulomatous folliculitis[16]
Chronic localized urticaria[51]

nuclei of these cells have large eosinophilic inclusions surrounded by a clear halo[52] (Figure 10). Neutrophilic invasion of the walls of affected vessels is often also seen, although unequivocal leukocytoclastic vasculitis is rare.[53] Less frequently, inclusions in the nuclei of endothelial cells have also been described in fibroblasts and macrophages as well as in the epithelium of eccrine ducts in cytomegalovirus infections.[54] In congenital cytomegalovirus infections, extramedullary hematopoiesis may be present in the skin.[55]

The presence of cytomegalovirus in cutaneous lesions may be confirmed by immunohistochemical analysis[56,57] or PCR techniques.[58]

Histopathology of Cutaneous Infection by the Epstein-Barr Virus

The Epstein-Barr virus, or Human herpesvirus 4, is a γ-herpes virus that causes infectious mononucleosis, hairy leukoplakia in patients with AIDS, a variety of lymphoproliferative processes, and nasopharyngeal lymphoepithelial carcinoma. In dermatology, it is also common to see a maculopapular rash in patients with mononucleosis who have been treated with ampicillin, because of the presence of immunoglobulin (Ig) G or IgM antibodies against penicillin. The rash is not attributable to IgE antibodies, as is the case in hypersensitivity reactions to penicillin. Histopathologic findings in these rashes are nonspecific. Observations include epidermal spongiosis and a superficial perivascular lymphohistiocytic infiltrate.

In hairy leukoplakia at the edges of the tongue, acanthosis with parakeratosis can be observed, along with large, pale keratinocytes particularly in superficial epithelial strata, and a variety of types of intranuclear inclusions.

Histopathology of Herpesvirus-6 and Herpesvirus-7 Skin Lesions

Human herpesvirus types 6 and 7 are γ-herpes viruses. Human herpesvirus 6 produces exanthem subitum, an infection also known as roseola infantum or the sixth disease of childhood. Human herpesvirus 7 has been linked to the reactivation of exanthem subitum caused by the type 6 virus and to some cases of pityriasis rosea, also known as Gilbert disease.

Histopathologic findings are nonspecific. Epidermal spongiosis is observed. Some degree of vacuolar degeneration might be present in the basal layer of the epidermis along with superficial perivascular lymphocytic infiltrate as in other viral exanthems.

Histopathology of Kaposi Sarcoma

Herpesvirus type 8 has now been shown to be involved with the development of all the epidemiologic variants of Kaposi sarcoma.[59-61]

The initial patch stage of Kaposi sarcoma is characterized by relatively subtle histopathologic findings that may be confused with an inflammatory process.[62] Under low magnification, a discrete inflammatory infiltrate of mononuclear cells can be observed perivascularly in both superficial and deeper layers of the lesion, along with an increase in the number of irregularly shaped vascular spaces, with narrow lumens and slits, with flattened endothelial cells lining small vessels and scattered through

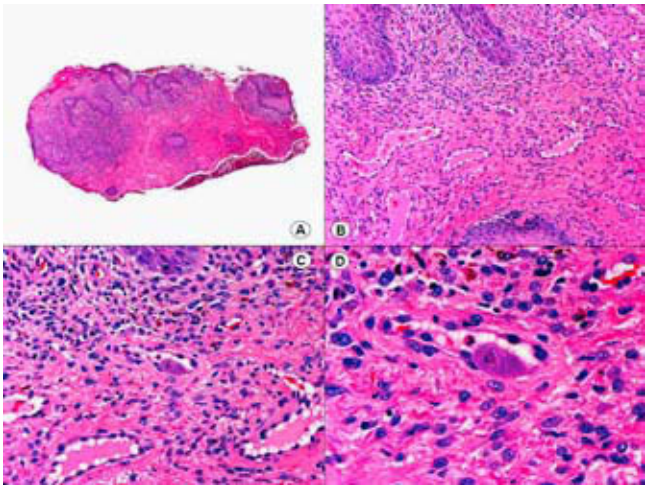

Figure 10 Histopathology of a genital lesion due to cytomegalovirus, showing typical inclusions in endothelial cells. (Hematoxylin-eosin stain; A, magnification ×10; B, ×40; C, ×200; D, ×400).

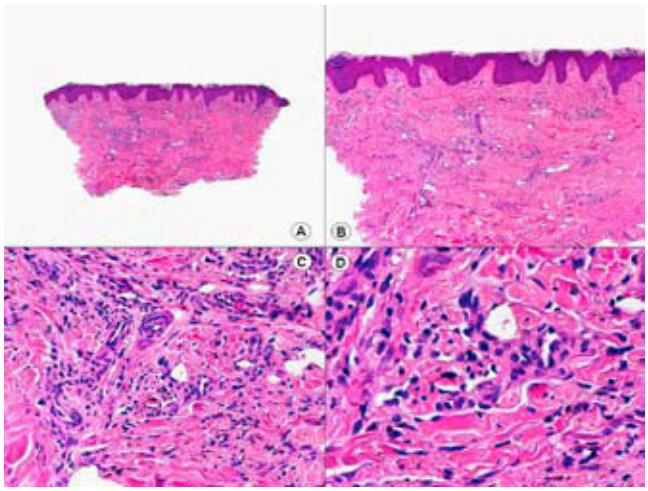

Figure 11 Histopathology of a Kaposi sarcoma patch showing spindle cells dissecting dermal collagen bundles. (Hematoxylin-eosin stain; A, magnification ×10; B, ×40; C, ×200; D, ×400).

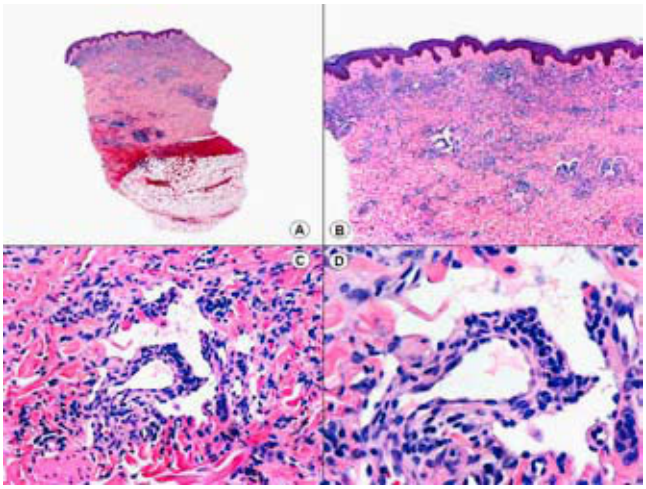

Figure 12 Histopathology of a Kaposi sarcoma plaque. The so-called promontory sign is visible. Some plasma cells are present in the infiltrate. (Hematoxylin-eosin stain; A, magnification ×10; B, ×40; C, ×200; D, ×400),

the entire thickness of the dermis (Figure 11). These irregularly shaped, thin-walled vascular spaces tend to surround blood vessels as well as nerve and adnexal structures of the dermis; when they dissect pre-existing capillaries the so-called promontory sign appears[63] (Figure 12). The inflammatory infiltrate appearing throughout the lesion mainly consists of lymphocytes and plasma cells; the latter are a finding that should lead to suspicion of Kaposi sarcoma in all incipient vascular lesions with irregularly shaped vessels and thin walls.[63] On rare occasions, the newly formed vessels are grouped into lobules, making the lesion resemble a small hemangioma. Another characteristic feature of Kaposi sarcoma lesions in their initial stages is the presence of scattered necrotic endothelial cells, which may be observed under either an optical microscope[64] or an electron microscope.[65] Hemosiderophages are also present in abundance, scattered in the stroma. These histopathologic findings that characterize the early stages of these lesions have also been described as present in apparently normal skin areas of patients with Kaposi sarcoma elsewhere, supporting the view that this disease is a generalized, diffuse process from the onset.[66,67]

Plaque lesions tend to affect the entire thickness of the dermis and they often spread to superficial areas of the subcutaneous cellular tissue. Spindle cells, arranged in fascicles between collagen bundles of the dermis and around newly formed vascular channels, become more numerous in this stage. These cells also line irregularly shaped slit-like or narrow vascular channels that contain a single blood vessel. Cellular atypia is not usually observed and mitotic count is very low.

When the number of spindle cells increases, Kaposi sarcoma lesions form nodules. The spindle cells then group themselves in intersecting fascicles with red blood cells scattered in the intercellular fluid (Figure 13). The degree of pleomorphism and cell atypia in these nodules is greater and some mitoses can be seen, although the number is not usually large. However, on rare occasions, particularly in the African variant of the disease, lesions may be made up of highly atypical spindle cells, and there may be a large number of mitoses observed. The presence of so-called hyaline globules is a finding that is fairly typical, though not strictly specific to Kaposi sarcoma. This observation is more common in plaque lesions or nodules but may be found during any phase of the disease. The globules, which stain positive with the periodic acid-Schiff technique and are diastase resistant, are eosinophilic spheres measuring between 1 and 10 μm and can be found both inside and outside cells. It seems that hyaline globules are red blood cells that have degenerated from phagocytes and that are included within phagolysosomes of neoplastic cells.[68,69] In any case, these structures should not be considered specific to Kaposi sarcoma, given that they have been described in other contexts of vascular proliferation such as angiosarcomas, pyogenic granulomas, or granulation tissue.[69]

On rare occasions when Kaposi sarcoma skin lesions are bullous, histopathologic findings mimic those of a lymphangioma given the presence of irregularly shaped, thin-walled vessels lined with a broken line of flattened endothelial cells; red blood cells are found neither inside the vessels nor outside in the stroma[70,71] (Figure 14). The absence of hemosiderin deposits and the scarcity of spindle cells are other observations that make these globules similar in appearance to lymphangiomas. The lymphangiomatous pattern can be found focally in lesions that are otherwise typical of Kaposi sarcoma; in fact we have observed patients with classic Kaposi sarcoma in whom some lesions showed this pattern while other lesions from the same patient had more typical Kaposi characteristics, with numerous extravasated red blood cells and abundant hemosiderin deposition. It has been suggested that chronic lymphoedema or a history of

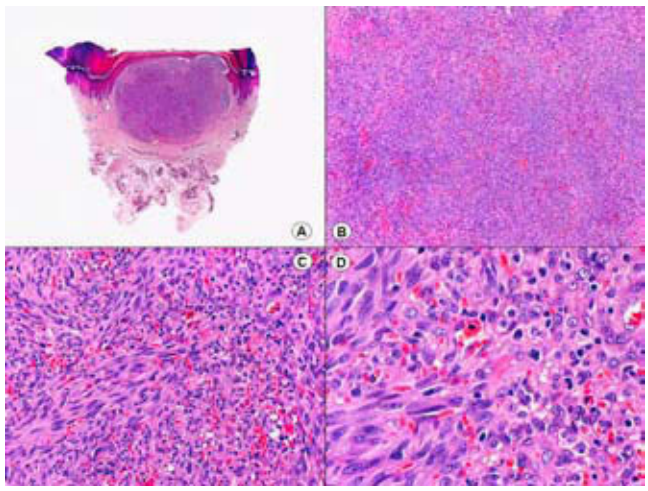

Figure 13 Histopathology of a solid Kaposi sarcoma nodule made up of spindle cells. A few red blood cells can be seen among the spindle cells. (Hematoxylin-eosin stain; A, magnification ×10; B, ×40; C, ×200; D, ×400).

radiotherapy applied to the affected area may favor the development of Kaposi sarcoma lesions that are reminiscent of lymphangioma.

Histogenetic evidence currently indicates that Kaposi sarcoma results from the proliferation of lymphatic endothelial cells, given that immunohistochemical analysis demonstrates that the proliferating cells express lymphatic markers (vascular endothelial growth factor receptor 3, podoplanin, lymphatic vessel endothelial hyaluronan receptor 1, and prospero-related homeobox protein 1).[72-75] Immunohistochemistry can also demonstrate the presence of herpesvirus 8 in the nuclei of proliferating cells in Kaposi sarcoma lesions in all its epidemiologic variants and from the earliest phases of the process[76] (Figures 15 and 16).

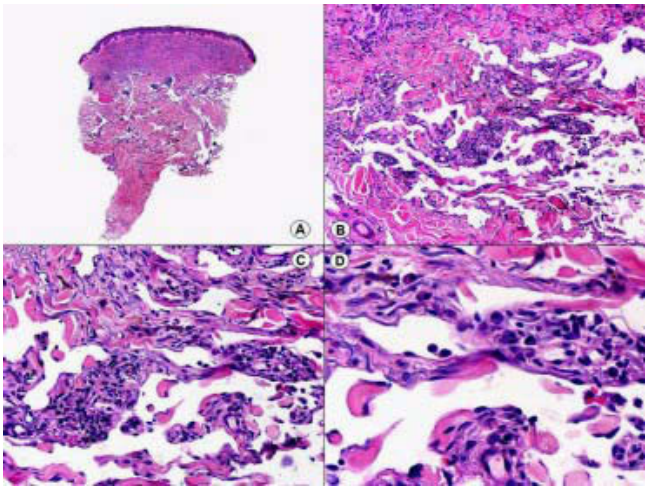

Figure 14 Histopathology of the so-called lymphangiomatous variant of Kaposi sarcoma, showing irregularly shaped vessels resembling lymph vessels dissecting the collagen bundles of the reticular dermis. (Hematoxylin-eosin stain; A, magnification ×10; B, ×40; C, ×200; D, ×400).

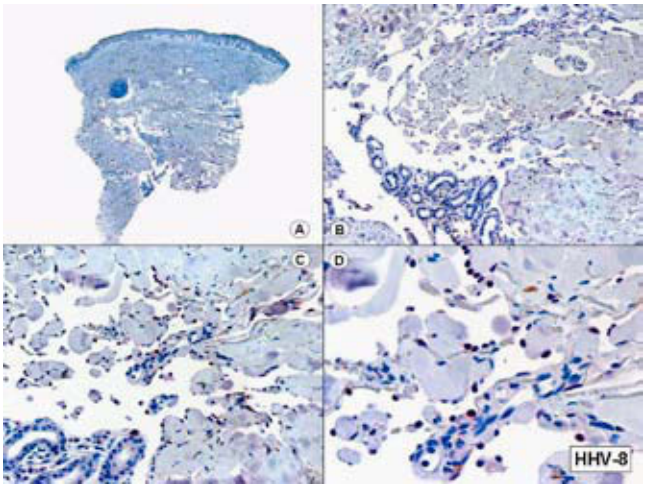

Figure 15 Immunohistochemical staining for human herpesvirus type 8 in the lesion classified as the so-called lymphangiomatous variant of Kaposi sarcoma. Some nuclei of neoplastic cells show positive. (A, magnification ×10; B, ×40; C, ×200; D, ×400).

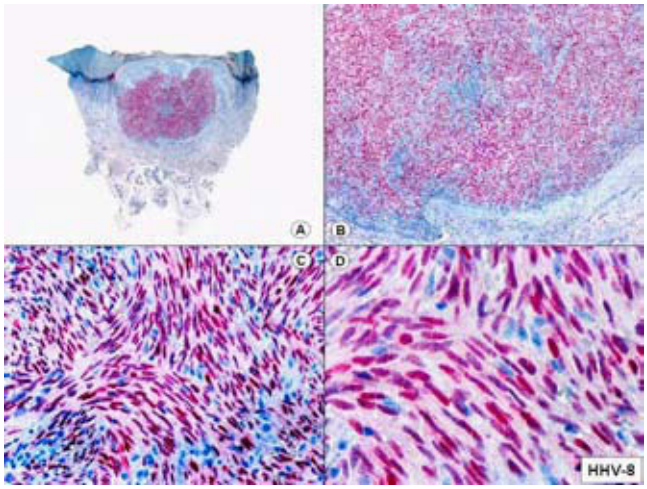

Figure 16 Immunohistochemistry for human herpesvirus type 8 of a Kaposi sarcoma nodule in which most neoplastic cells stain positive. (A, magnification ×10; B, ×40; C, ×200; D, ×400).

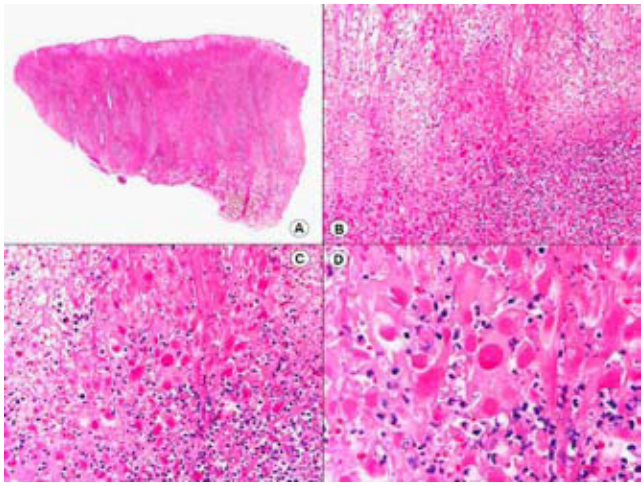

Figure 17 Histopathology of an orf ulcer (contagious ecthyma), showing abundant eosinophilic inclusion bodies in epidermal epithelial cells. (Hematoxylin-eosin stain; A, magnification ×10; B, ×40; C, ×200; D, ×400).

Histopathology of Orf Ulcer (Contagious Ecthyma), Milker's Nodule, and Molluscum Contagiosum

Skin infections due to parapoxvirus also have characteristic histopathology.

In contagious ecthyma, observations are irregular acanthosis with large keratinocytes that have abundant cytoplasm and appear pale because of ballooning; they are found mainly in superficial dermal layers[77] (Figure 17). Eosinophilic inclusions in cytoplasm are often seen.[78]

Epithelial damage is sometimes more intense, showing so-called spongiform degeneration of the epidermis and epithelium of hair follicles; this pattern consists of intense vacuolization of epithelial cells with eosinophilic granules of different sizes.[78] The dermis contains marked proliferation of blood vessels, which can at times be intense enough to mimic a hemangioma, and there is an inflammatory infiltrate of lymphocytes, eosinophils, histiocytes, and plasma cells.[79] Atypical CD30-positive lymphocytes are sometimes seen,[80] but should not be mistaken for an indication of primary cutaneous CD30-positive anaplastic large cell lymphoma.

The histopathology of milker's nodule is very similar, although the entire thickness of the epidermis is less often affected than it is in orf ulcers[78,81] (Figure 18).

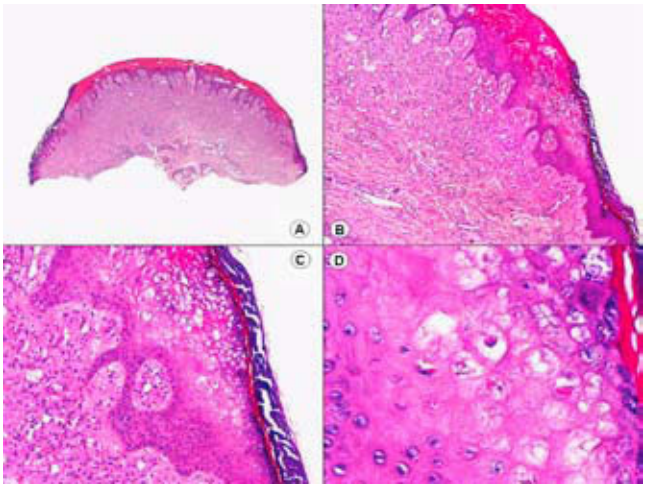

Figure 18 Histopathology of a milker's nodule, showing ballooning of epidermal keratinocytes and the presence of inclusion bodies. (Hematoxylin-eosin stain; A, magnification ×10; B, ×40; C, ×200; D, ×400).

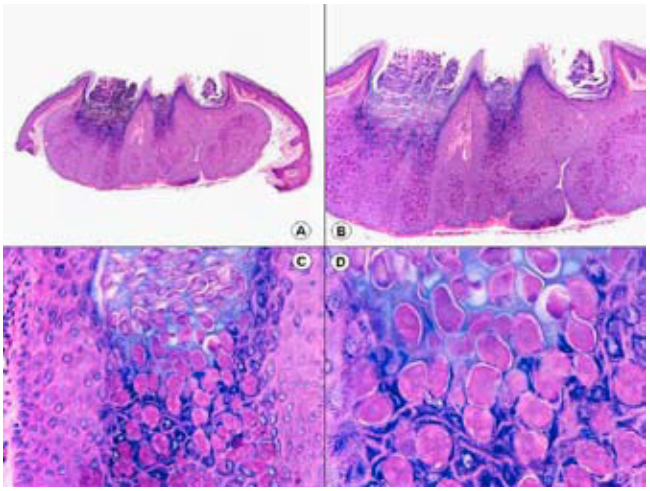

Figure 19 Histopathology of a molluscum contagiosum lesion which shows the typical presence of inclusion bodies. (Hematoxylin-eosin stain; A, magnification ×10; B, ×40; C, ×200; D, ×400).

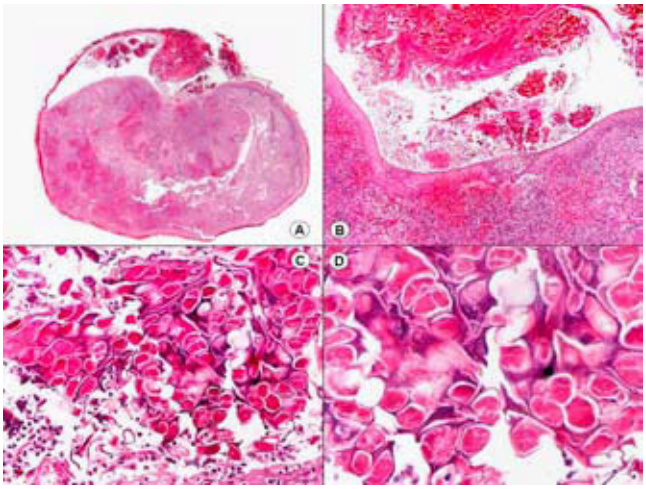

Figure 20 Histopathology of a pseudolymphoma associated with molluscum contagiosum. The characteristic inclusion bodies are in evidence. (Hematoxylin-eosin stain; A, magnification ×10; B, ×40; C, ×200; D, ×400).

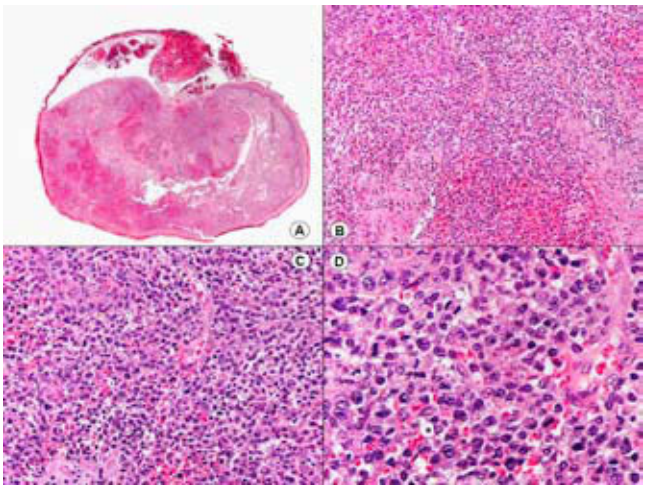

Figure 21 Histopathology of a pseudolymphoma associated with molluscum contagiosum. Atypical lymphocytes and numerous mitoses can be seen in the infiltrate around the lesion. (Hematoxylin-eosin stain; A, magnification ×10; B, ×40; C, ×200; D, ×400).

Molluscum contagiosum lesions contain epithelial nodules that open onto the surface of the skin and that penetrate the dermis[82] (Figure 19). The epithelium of follicular infundibula are often involved, and in such cases the lesion may appear cystic.[82,83] Many keratinocytes contain characteristic cytoplasmic inclusion bodies that increase in size from the basal layers to the more superficial layers of the epidermis. Basophil counts also increase toward more superficial layers. The inflammatory infiltrate is scant in the underlying dermis, although cases in which there is an intense lymphocytic infiltrate may resemble cutaneous leukemia[84] or a cutaneous CD30-positive lymphoma[85,86] (Figures 20 and 21).

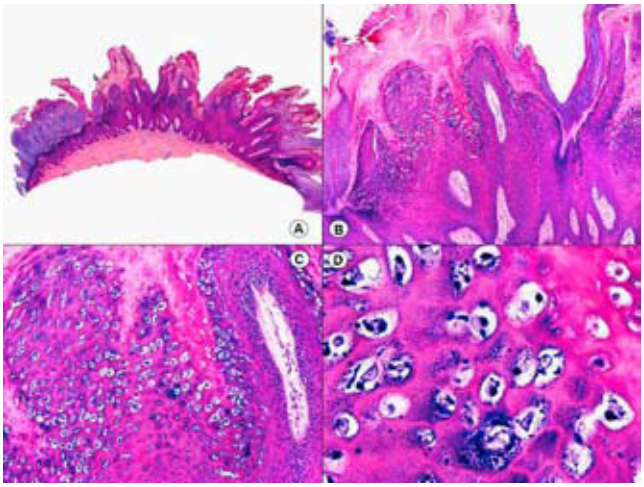

Figure 22 Histopathology of a common wart showing papillomatosis and koilocytes. (Hematoxylin-eosin stain; A, magnification ×10; B, ×40; C, ×200; D, ×400).

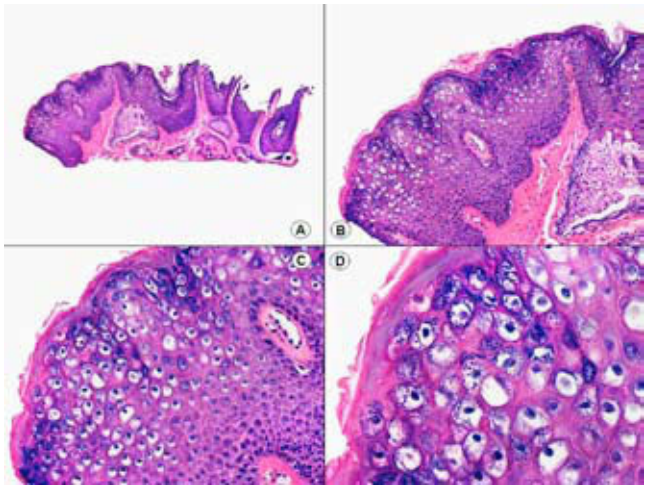

Figure 23 Histopathology of a plane wart displaying intense vacuolization of keratinocytes in higher epidermal strata. (Hematoxylin-eosin stain; A, magnification ×10; B, ×40; C, ×200; D, ×400).

Histopathology of Verrucous Lesions

Skin infections caused by human papillomavirus differ according to clinical variant.

The common wart shares its histopathologic profile with the filiform mosaic plantar warts. Structurally, these warts are characterized by papillomas with acanthosis and hyperkeratosis, with parakeratotic columns extending from the points on the papillomatous surface[87] (Figure 22). The papillomas take on a radial pattern, with confluence of the underlying epidermal rete ridges toward the center of the lesion. Under higher magnification, vacuolar cell changes can be seen. Cells have small, hyperchromatic nuclei surrounded by a clear halo and pale cytoplasm. Keratohyaline granules are not present. These vacuoles are more evident at papillomatous elevations in the granular layer. Parakeratotic columns continue in the stratum corneum. The cells of these columns have rounder nuclei than those usually found in other forms of parakeratosis. Depressions in the stratum granulosum contain granular cells with collections of degranulated keratohyaline granules that are rough, thickened. Staining is variable. All these histopathologic findings are less evident in or entirely absent from long-standing warts but they can be easily detected in recently formed lesions.

Filiform warts are similar, but with more intense hyperkeratotic and papillomatous formations and capillary dilation in the papillary dermis alternating with small hemorrhagic points.

Plane, or flat-topped, warts present the same hyperkeratosis and acanthosis seen in other viral warts, but they lack papillomatous and parakeratotic structures. The most characteristic finding in this variety is thickening of the granular layer, where the cells are larger than expected, vacuolized, and have small, centrally located, and basophilic nuclei (Figure 23). Vacuolization is also seen in corneocytes in the stratum corneum.

Mosaic plantar warts are also histopathologically similar to common warts. Other plantar warts, such as the myrmecia variety, in contrast, have specific features.[87-89] Numerous intracytoplasmic eosinophilic granules can be seen throughout the epidermis of myrmecia warts. These granules increase in size toward the surface, where they fuse to form inclusion bodies that are homogenously colored but irregularly shaped (Figure 24). The inclusion bodies envelop the cell nuclei or may be separated from it by a clear, irregularly shaped halo. Unlike molluscum contagiosum lesions, myrmecia warts do not have their cell nuclei replaced by cytoplasmic inclusions. These abnormalities can also been found in corneocytes in the stratum corneum.

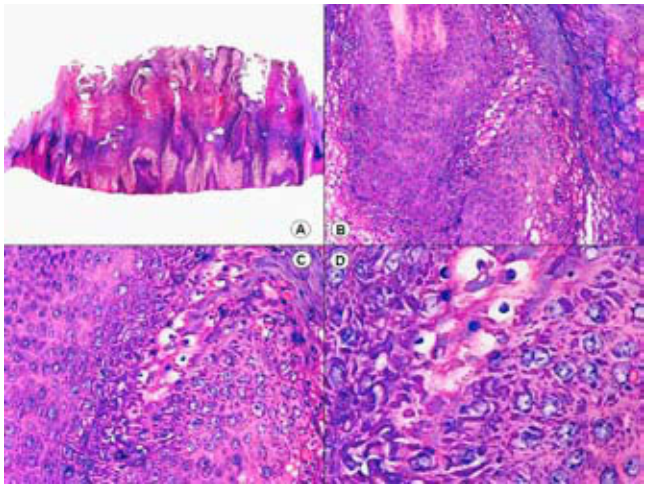

Figure 24 Histopathology of a myrmecia plantar wart. Numerous eosinophilic granules can be seen in the cytoplasm of cells throughout the epidermis. The granules are larger in higher strata, where they fuse to form inclusion bodies that are homogenously colored and irregularly shaped. (Hematoxylin-eosin stain; A, magnification ×10; B, ×40; C, ×200; D, ×400).

Condyloma acuminata lesions show marked acanthosis and papilloma formation, but hyperkeratosis is lacking or

very faint (Figure 25). Unlike warts in other locations, these anal or genital warts have a more basophilic staining of the acanthotic epithelium and contain a considerable number of mitoses.[90] Vacuoles are also in evidence. It should be remembered, however, that normal cells of the mucosal epithelium are typically vacuolated; the vacuoles of anal-genital warts, in contrast, can be found even in the deeper strata of the epidermis. The giant Buschke-Löwenstein condyloma is a verrucous carcinoma found on the genitals. The histopathology of this lesion is similar to that of other verrucous carcinomas[91] (Figure 26).

Bowenoid papulosis may be histologically indistinguishable from Bowen disease, although atypia and intraepidermal dysplasia are traditionally thought to be more circumscribed rather than distributed throughout the thickness of the epidermis[92,93] (Figure 27). Other findings that are more typical of bowenoid papulosis than of Bowen disease are the presence of multinucleated monster cells, more abundant vacuolization of the cytoplasm, and the presence of a well developed stratum granulosum without cellular atypia.

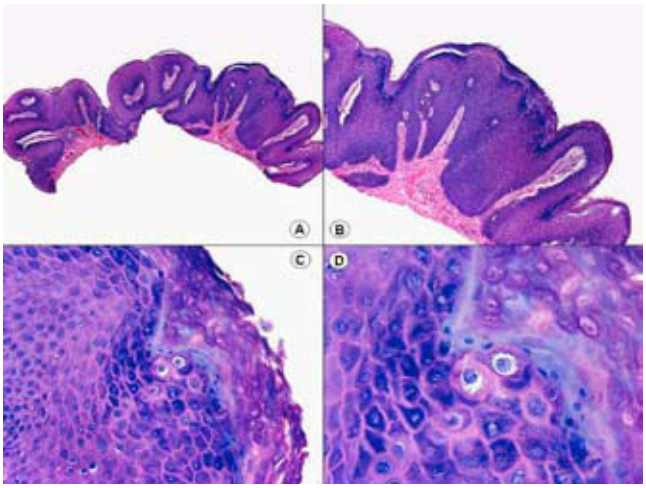

Figure 25 Histopathology of a condyloma acuminatum with a more basophilic epithelium than is seen in other common warts. Koilocytes are scarce. (Hematoxylin-eosin stain; A, magnification ×10; B, ×40; C, ×200; D, ×400).

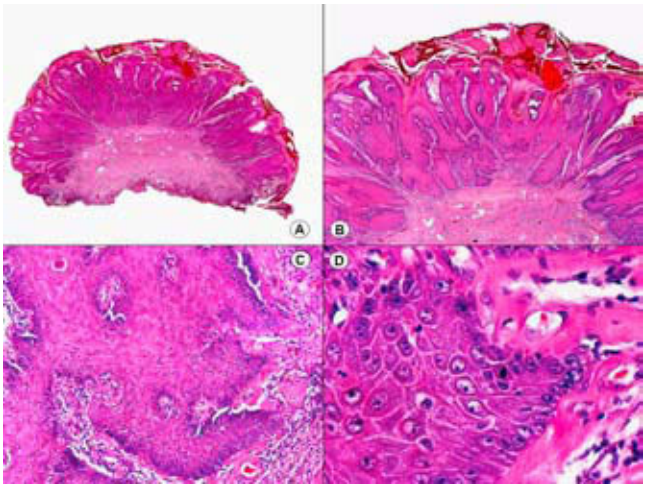

Figure 26 Histopathology of a giant Buschke-Löwenstein condyloma with an exophytic architecture and the cytology of a verrucous carcinoma. (Hematoxylin-eosin stain; A, magnification ×10; B, ×40; C, ×200; D, ×400).

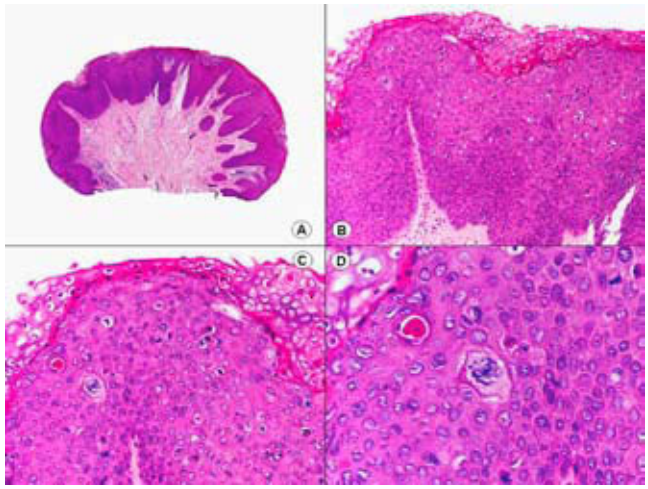

Figure 27 Histopathology of bowenoid papulosis, showing atypia and intraepidermal dysplasia. These findings are more focal than those seen in Bowen disease. Here they do not affect the entire thickness of the epidermis. (Hematoxylin-eosin stain; A, magnification ×10; B, ×40; C, ×200; D, ×400).

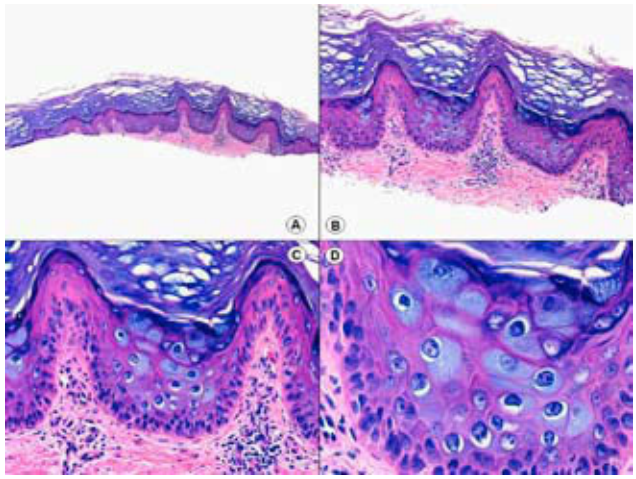

Figure 28 Histopathology of epidermodysplasia verruciformis. Evident are large, swollen keratinocytes that are irregularly shaped. The cytoplasm is abundant and basophilic. (Hematoxylin-eosin stain; A, magnification ×10; B, ×40; C, ×200; D, ×400).

Epidermodysplasia verruciformis shows histopathologic features similar to those of plane warts, although in dysplasia vacuolized cells can be seen in deeper epidermal layers.[94] Included in the series of cellular changes traditionally described for epidermodysplasia verruciformis are large-sized keratinocytes that are swollen, irregularly shaped and have an abundant, basophilic cytoplasm[95] (Figure 28). For some authors, cytopathologic observations like these point to papillomavirus infection in immunocompromised patients.

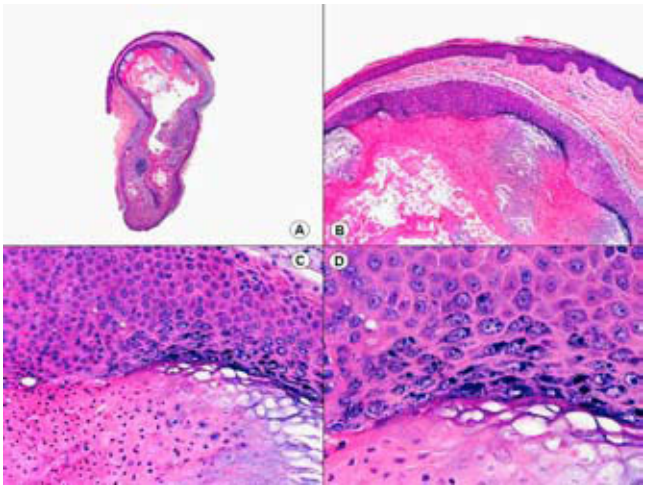

Figure 29 Histopathology of a verrucous cyst. The epithelial wall has a papillomatous luminal lining, with acanthosis with marked hypergranulosis of rough, thick and irregularly shaped keratohyaline granules. (Hematoxylin-eosin stain; A, magnification ×10; B, ×40; C, ×200; D, ×400).

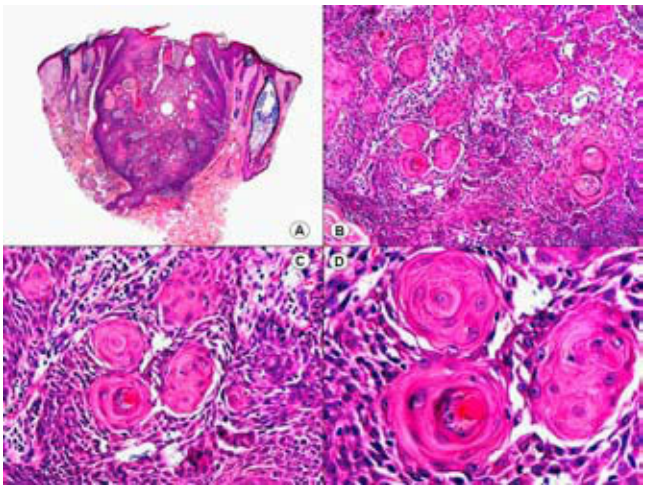

Figure 30 Histopathology of inverted follicular keratosis showing an endophytic lesion whose general architecture is similar to that of a common wart. Abundant squamous eddies can be seen scattered throughout a squamous epithelium. (Hematoxylin-eosin stain; A, magnification ×10; B, ×40; C, ×200; D, ×400).

The epithelial wall of a verrucous cyst has a papillomatous luminal lining, showing acanthosis and marked hypergranulosis of rough, thick, and irregularly shaped keratohyaline granules[96] (Figure 29).

Inverted follicular keratosis has the same general architecture of a common wart, but growth is more endophytic than exophytic in the former; a peculiarity of this type of keratosis is the arrangement of squamous cell swirls, or eddies, arising from hyperplastic follicular infundibula[97] (Figure 30). The lesion usually has an overlying layer of orthokeratotic hyperkeratosis, but as in other common wart variants it is not unusual to find parakeratotic columns rising vertically from points on the dermal papillae. The stratum granulosum is typically thickened, at least focally, and it is not unusual to see thick keratohyaline granules. Noteworthy in the underlying dermis are congested, twisting capillaries that contain red blood cells in abundance, and also a predominantly lymphocytic inflammatory infiltrate located around the vessels. There is no consensus on the origin of the so-called squamous eddies evident in cross-sections of epithelial lobules of inverted follicular keratosis lesions, although serial slices of these structures often show them to be in contact with an adjacent sebaceous gland. Therefore, they may be hyperplastic sebaceous ducts trapped inside the lesion, with squamous metaplasia developing later. In any case, these squamous eddies are not specific to inverted follicular keratosis, as they can be seen fairly often in irritated seborrheic keratosis and, more sporadically, in keratoacanthomas.

Trichilemmoma has the general architecture of a common wart and under low magnification seems to consist of 1 or more hyperplastic follicular infundibula whose epithelium displays differentiation similar to that of an external root sheath of the inferior segment of active hair follicles. Several adjacent follicular infundibula are usually involved. Most of these lesions have both an exophytic and endophytic component and they generally adopt a vertical position. The surface of the lesion is discretely papillomatous or markedly verrucous. Hypergranulosis may sometimes be seen in the depressions of papillae on the lesion surface, while the vertices of these papillae have parakeratotic columns, findings reminiscent of common warts.[98,99] Adnexal epithelial cords are often found around the edges of these lesions. A trichilemmoma, properly categorized, is formed of solid epithelial lobules of clear, monomorphic cells with eosinophilic cytoplasm that is pale

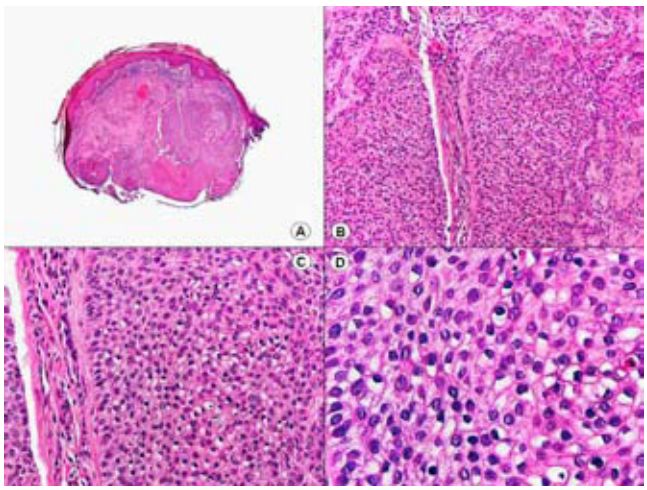

Figure 31 Histopathology of a trichilemmoma consisting of solid epithelial lobules made up of clear, monomorphic cells with pale or optically transparent eosinophilic cytoplasm due to abundance of glycogen and a small nucleus that has a vesicular appearance, is round and excentrically located. In many areas, cell threads show peripheral palisading and lie over a thick basement membrane. (Hematoxylin-eosin stain; A, magnification ×10; B, ×40; C, ×200; D, ×400).

or optically transparent due to abundance of glycogen and a small-sized nucleus that has a vesicular appearance, is round, and excentrically located (Figure 31). In many areas, threads of cells showing peripheral palisading lie over a thick basement membrane similar to the vitreous membrane that surrounds a normal hair follicle. On occasions, a cross-section of these epithelial lobules made up of clear cells reveals squamous eddies similar to those of inverted follicular keratosis, demonstrating that these 2 lesions are closely related.[98] A trichilemmoma has a fairly scant stroma made up of collagen fibers. In dermal papillae, the collagen contains dilated, twisted capillaries with an abundance of red blood cells. There is often a discrete lymphocytic inflammatory infiltrate in the dermis underlying the lesion. So-called desmoplastic trichilemmoma[100,101] has a configuration that is generally similar to the preceding type, but in some areas of the lesion, particularly deep portions, the epithelial lobules are prolonged by cords of pale or basaloid epithelial cells that are trapped with sclerotic collagen bundles in a desmoplastic stroma. This pattern can cause problems of differential histopathologic diagnosis, particularly in relation to morpheaform basal cell carcinoma (Figure 32). However, the general architecture of these desmoplastic trichilemmomas is that of a benign lesion. In addition to areas where epithelial cords are embedded in the desmoplastic stroma solid clear-cell epithelial lobules can be found on the surfaces and sides of the lesion. They display peripheral cell palisading overlying the thick basement membrane—characteristic of trichilemmoma.

In focal epithelial hyperplasia (Heck disease), the histopathologist sees acanthosis, papillomatosis with openings in the interpapillary ridges at deeper layers of the epithelium, as well as vacuolized cells in superficial layers. A characteristic finding is the scattered presence of so-called mitosoid cells, which are keratinocytes with irregularly shaped, hyperchromatic nuclei that simulate mitoses but that are in fact degenerated nuclei without mitotic ability[102,103] (Figure 33).

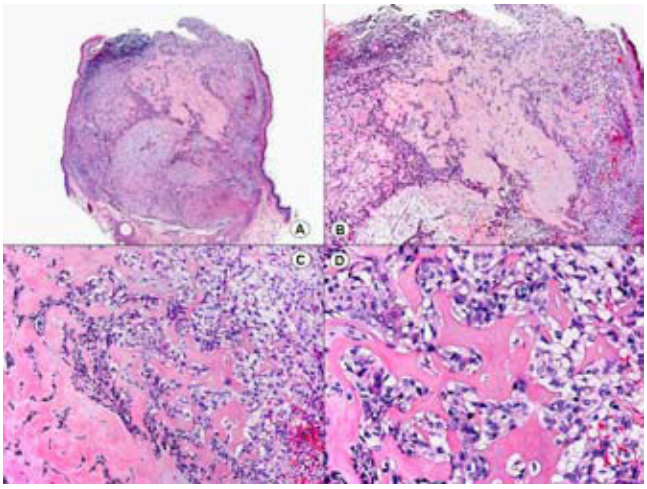

Figure 32 Histopathology of a desmoplastic trichilemmoma with a configuration that is generally similar to that of a common trichilemmoma. However, some areas, particularly in the deeper portions of the lesions, the epithelial lobules are prolonged by cords of pale or basaloid epithelial cells that are trapped in a desmoplastic stroma with sclerotic collagen bundles. (Hematoxylin-eosin stain; A, magnification ×10; B, ×40; C, ×200; D, ×400).

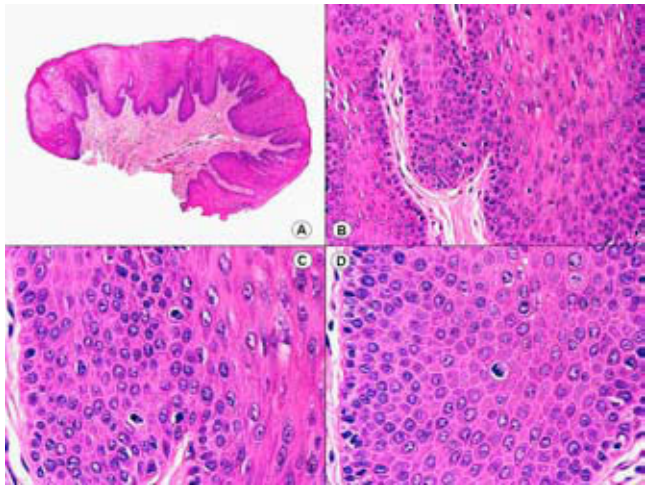

Figure 33 Histopathology of a focal epithelial hyperplastic lesion (in Heck disease) displaying acanthosis, with openings in the interpapillary ridges at deeper layers and the presence of vacuolized cells in superficial layers. A scattering of so-called mitosoid cells is a characteristic finding. These cells are keratinocytes with irregularly shaped, hyperchromatic nuclei that simulate mitoses but that are in fact degenerated nuclei without mitotic ability. (Hematoxylin-eosin stain; A, magnification ×10; B, ×40; C, ×200; D, ×400).

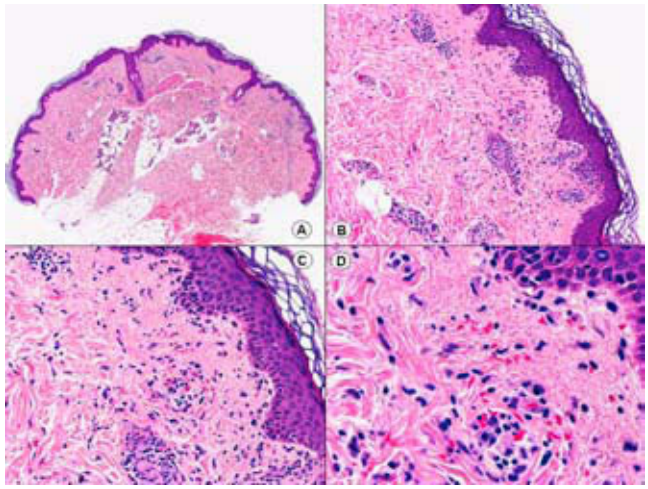

Figure 34 Histopathology of a lesion pertaining to purpuric gloves-and-socks disease. Evident features are slight epidermal spongiosis, parakeratotic areas, and a small perivascular infiltrate around the superficial vascular plexus of the dermis. Extravasated red blood cells can also be seen around superficial dermal capillaries. (Hematoxylin-eosin stain; A, magnification ×10; B, ×40; C, ×200; D, ×400).

Histopathology of Cutaneous Infections Due to Parvovirus B19

Generally speaking, the histopathologic findings in infectious erythema and purpuric gloves-and-socks syndrome are nonspecific. The histopathologist will note varying degrees of epidermal spongiosis, parakeratotic foci, and a discrete perivascular infiltrate around a superficial vascular plexus in the dermis. Gloves-and-socks syndrome also usually presents with extravasated red blood cells around superficial dermal capillaries (Figure 34). The presence of parvovirus B19 in the endothelial cells of these capillaries can sometimes be demonstrated immunohistochemically (Figure 35).

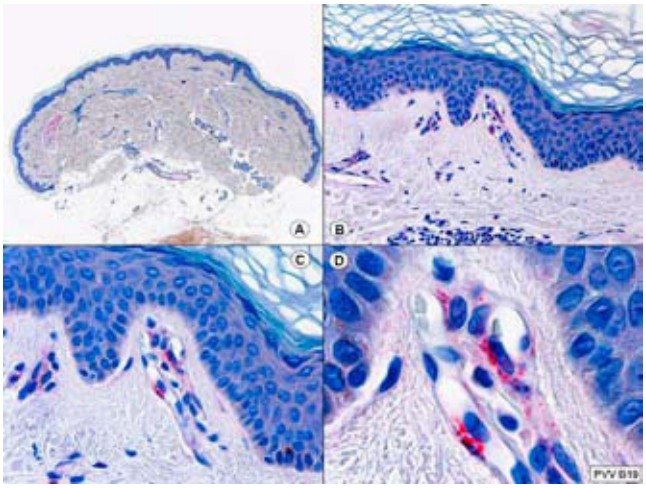

Figure 35 Immunohistochemical staining for the parvovirus B19, showing positivity in some endothelial cells of capillaries in the superficial dermis. (Immunohistochemistry for parvovirus B19; A, magnification ×10; B, x40; C, ×200; D, ×400).

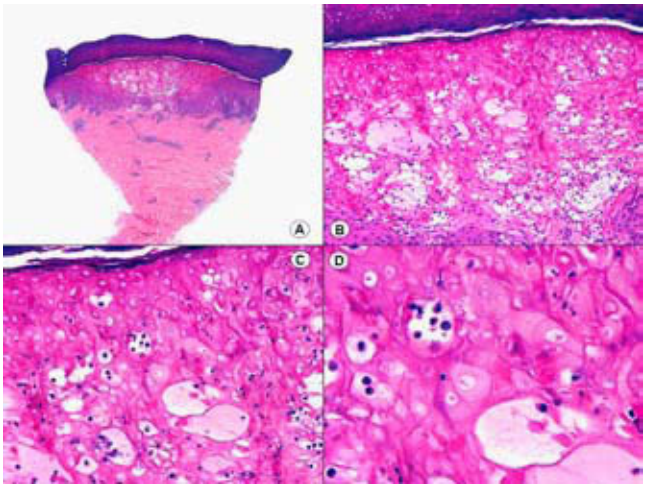

Figure 36 Histopathology of a lesion in hand-foot-mouth disease, showing intraepidermal vesicles with marked ballooning of keratinocytes at higher layers. (Hematoxylin-eosin stain; A, magnification ×10; B, ×40; C, ×200; D, ×400).

Histopathology of Hand-Foot-Mouth Disease

The cutaneous lesions of hand-foot-mouth disease due to coxsackievirus A16 consist of intraepidermal vesicles with marked ballooning of keratinocytes in higher layers of recent-onset lesions (Figure 36) and reticular degeneration throughout the dermis in longer-standing ones. Papillary edema can be seen in the dermis along with a discrete, predominantly lymphocytic inflammatory infiltrate mainly positioned around vessels.

Conflicts of Interest

The authors declare they have no conflicts of interest.

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