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Pathology of the Cutaneous Vasculitides: A Comprehensive Review

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1. Introduction

Vasculitis has historically been poorly defined and the histological and clinical manifestations are protean, further complicating the diagnostic process. The definitive diagnosis is made by evidence of histologic effacement of a vessel with associated transumural inflammatory infiltrate of that vessel. Vasculitis can be a primary process or secondary to disseminated intravascular coagulation, ulceration, arthropod assault, and/or suppurative infiltrates (for example pyoderma gangrenosum). Vasculitis must further be distinguished from vasculopathies, particularly livedoid vasculopathy and connective tissue diseases (namely scleroderma and systemic lupus erythematosus) in which the primary process is vascular fibrin thrombi of the upper dermal vessels. A necrotizing vasculitis resulting secondary to the thrombotic process can occur, blurring the lines between true vasculitis and vasculopathy. Very few vasculitic processes have pathognomonic histological findings. Often times the dermatopathologist and clinician must work in concert and combine clinical, histological, and laboratory data to determine what the primary process is. As previously stated, histological evidence of inflammatory infiltrate within the vessel wall must be seen in order to diagnose vasculitis. Associated findings include fibrinoid necrosis, endothelial swelling, and endothelial cell apoptosis (Carlson, et al., 2005). Other secondary changes including extravasation of red blood cells, necrosis, ulceration, and neovascularization suggest that there has been vascular damage (Carlson et al., 2005). Associated changes can also be seen in the sweat glands and include basal cell degeneration, necrosis, and basal cell hyperplasia (Akosa & Lampert, 1991). Changes in the adjacent tissue can aid the dermatopathologist in determining what the underlying etiology causing the vasculitis could be. Extravascular granulomas characterized by degenerating collagen bundles surrounded by eosinophils and flame figures ("red" granulomas) are seen in Churg Strauss Syndrome while extravascular granulomas characterized by degenerating collagen bundles surrounded by basophilic debris ("blue" granulomas) are seen in Wegener's granulomatosis and rheumatoid vasculitis (Carlson, 2010). Dermal lamellar fibrosis can be seen in erythema elevatum diutinum and granulomas faciale (Carlson et al., 2005). Direct immunofluorescence adds another important diagnostic piece of information. Absence of immune complex deposition (pauci-immune vasculitis) is seen in Wegener's granulomatosis, microscopic polyangiitis, and Churg Strauss syndrome (Carlson, 2010).

Peri-vascular deposition of IgG, IgM, and/or C3 is seen in cutaneous leukocytoclastic angiitis, urticarial vasculitis, and connective tissue disease vasculitis (Carlson et al., 2005). Vascular deposits of IgA are found in Henoch Schonlein purpura while deposition of IgM is seen in cryoglobulinemic vasculitis (Carlson, 2010). Basement membrane zone deposition of immunoglobulins can be seen in urticarial vasculitis and connective tissue disease vasculitis (Carlson et al., 2005).

The most common classification system of vasculitides is based on the size of the affected vessel. While biopsy is required for definitive diagnosis, the size of the affected vessel correlates with the cutaneous lesions seen. Large vessel involvement manifests as limb claudication, absent pulses, aortic dilation, bruits, and/or asymmetric blood pressure (Chen & Carlson, 2008). Giant cell (temporal) arteritis and Takayasu's arteritis are examples of this (Carlson, 2010). Vasculitis involving medium sized (muscular) vessels manifest as subcutaneous nodules, deep ulcers, livedo reticularis, palmar or digital scars, digital gangrene, mononeuritis, erythematous nodules, and aneurysms (Chen & Carlson, 2008). Examples of this include polyarteritis nodosa, Kawasaki disease, and nodular vasculitis (Carlson, 2010). Small vessel vasculitis can be further subdivided into two categories: immune complex mediated vasculitis arising in small post-capillary venules or non-immune complex mediated vasculitis arising in small muscular arteries and arterioles. Small vessel vasculitis appears as purpura, erythema, urticaria, vesiculobullous lesions, superficial ulcers, and splinter hemorrhages (Chen & Carlson, 2008). Examples of this include cutaneous leukocytoclastic vasculitis, Henoch Schonlein purpura, urticarial vasculitis, Churg Strauss vasculitis, Wegener's granulomatosis, and microscopic polyangiitis (Carlson, 2010).

Biopsy location, depth, and timing must be taken into consideration by the clinician to increase the diagnostic yield. Since small vessels reside in the upper dermis while medium sized, muscular vessels are found in the deep dermis and subcutis, a punch or excisional biopsy is required to ensure adequate sampling of all vessel sizes (Carlson et al., 2005). Biopsies performed within 48 hours after the onset of lesions can show a neutrophilic, eosinophilic, or lymphocytic infiltration, depending on the underlying process (Chen & Carlson, 2008). However, after 48 hours, lymphocytes replace the other inflammatory cells, regardless of the underlying etiology and will therefore be non-diagnostic (Chen & Carlson, 2008). Fibrosis, luminal obliteration, and lamination of the vessel wall is seen in healed lesions of vasculitis (Chen et al., 2005). Biopsy from a patient with livedo racemosa must be taken from the center white areas rather then the peripheral red areas since this is where the vascular stenosis can be seen (Carlson, 2010). Biopsy of superficial ulcers should be taken from non-ulcerated skin or from the edge of the ulcer whereas biopsy of deep ulcers should be taken central to the ulcer and include subcutaneous tissue to increase the diagnostic yield of medium sized vessel vasculitis (Chen & Carlson, 2008).

2. Small vessel vasculitis

2.1 Immune complex mediated vasculitis in post capillary venules

2.1.1 Cutaneous leukocytoclastic angiitis

Cutaneous leukocytoclastic angiitis (CLA) is also known as cutaneous leukocytoclastic vasculitis, hypersensitivity vasculitis/angiitis, allergic vasculitis, and necrotizing vasculitis (Carlson & Chen, 2006). The Chapel Hill Consensus Conference (CHCC) defines CLA as an isolated cutaneous leukocytoclastic vasculitis in the absence of systemic vasculitis (Carlson et al., 2005). Patients are typically middle aged adults with a recent history of exercise in hot

weather (Chen & Carlson, 2008). Less than 10% of patients may present with renal or gastrointestinal involvement, however, this systemic vasculitis variant of CLA has yet to be formally recognized (Carlson, 2010). Etiology may be secondary to medications, viral upper respiratory infection, or collagen vascular diseases; however, in the majority of cases no etiology will be identified (Grunwald et al., 1997).

The cutaneous manifestations include crops of palpable purpura over the lower extremities associated with pruritus, stinging, tenderness, or burning (Chen & Carlson, 2008). Rarely patients may present with erythema and hemorrhagic bullae on the lower extremities (Carlson, 2010). Areas of ecchymoses and hyperpigmenation are seen as the lesions resolve over a period of 3-4 weeks (Chen & Carlson, 2008).

The general pathologic features of CLA on a skin biopsy include fibrin deposits, neutrophilic perivascular infiltration of small vessels, and nuclear debris (leukocytoclasia) (Carlson & Chen, 2006) (see Figures 1 and 2). Hemophagocytosis can also be seen (Draper & Morgan, 2007). The pathologic features of CLA change with temporal evolution. Early lesions are characterized by a neutrophil dominant vasculitis in the upper to mid dermis which then progresses to a mononuclear predominant vasculitis within 120 hours after the onset of the lesions (Zax et al., 1990) (see Figure 3). Epidermal involvement including vesicle formation and ulceration can also be identified (Grunwald et al., 1997). The healing lesions show regenerative endothelial cells, fibrin deposits within vessel walls, and a mild monocytic perivascular infiltrate (Grunwald et al., 1997) (see Figure 4). The other classic features of CLA including extravasation of erythrocytes, fibrinoid necrosis, and epidermal necrosis fade as the lesions age (Zax et al., 1990). Rarely a necrotizing venulitis can be seen extending through the mid and deep dermis (Carlson, 2010).

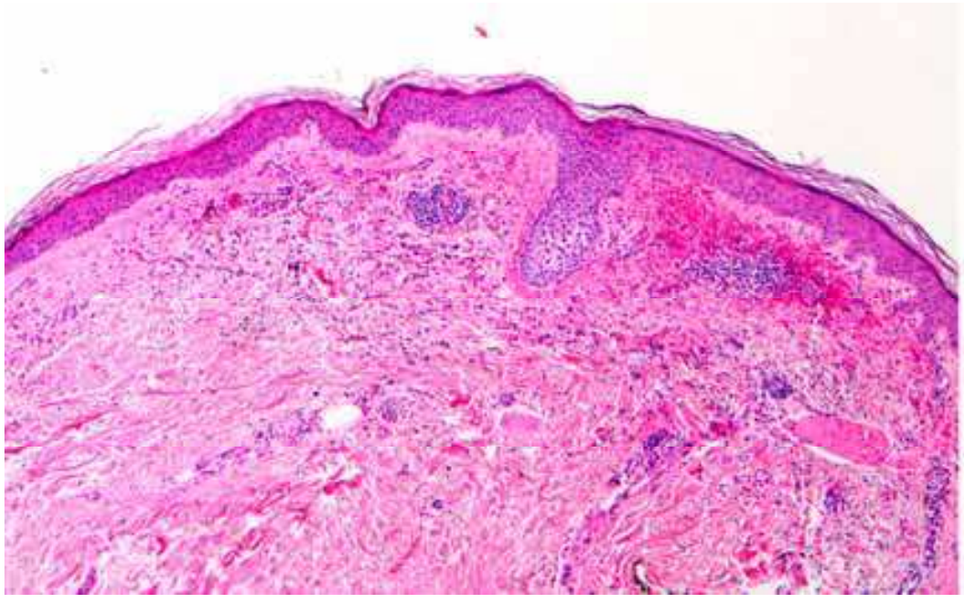


Fig. 1. Cutaneous Leukocytoclastic Angiitis. Small vessel vasculitides demonstrate many common features including fibrinoid necrosis, marked inflammation, leukocytoclasia and red cell extravasation (H&E, 40x).

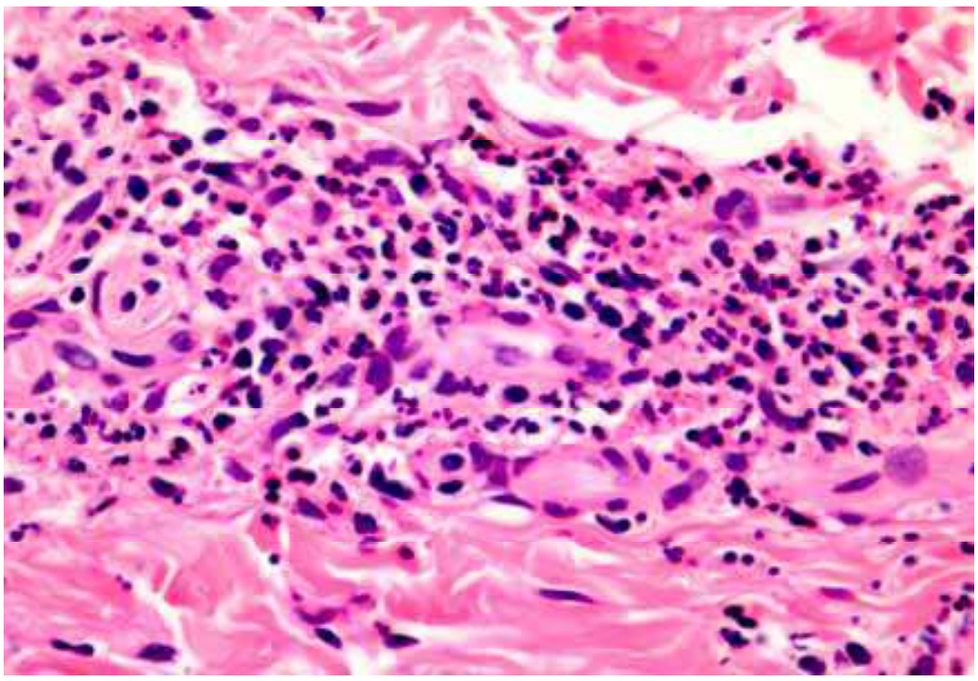


Fig. 2. Cutaneous Leukocytoclastic Angiitis. Neutrophilic perivascular infiltration of small vessels with accompanying leukocytoclasia consisting of karryorhectic nuclear debris (H&E, 400x).

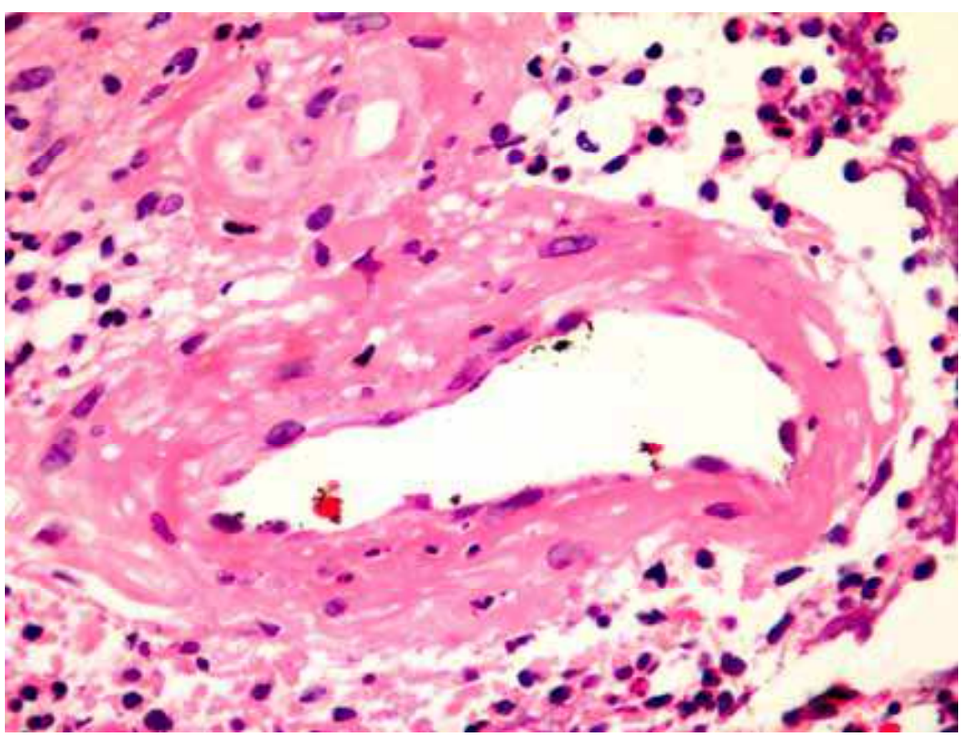


Fig. 3. Cutaneous Leukocytoclastic Angiitis. Fibrinoid necrosis of the vessel walls is characteristic (H&E, 400x).

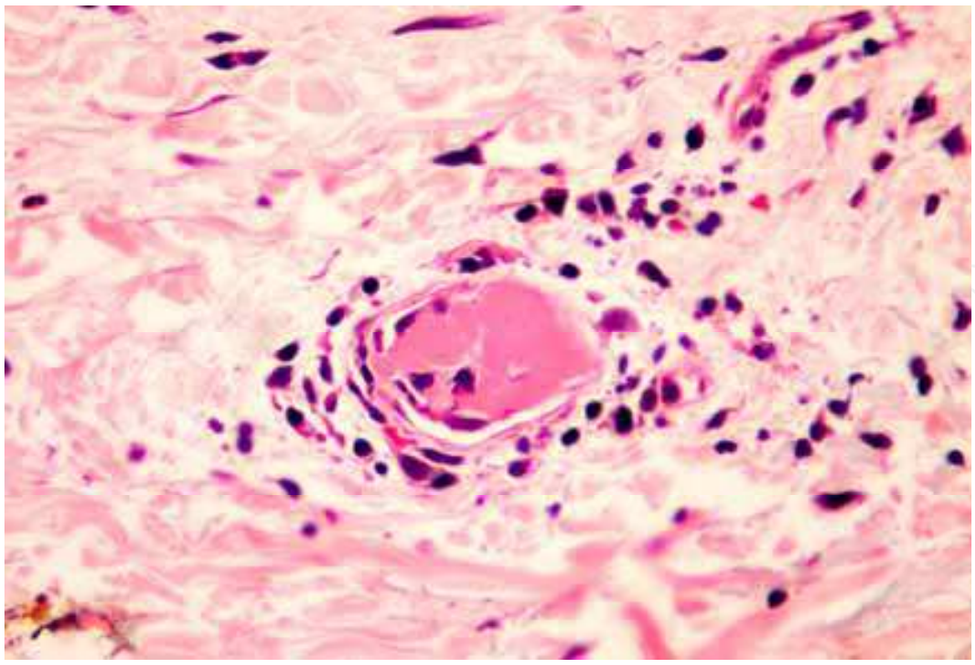


Fig. 4. Cutaneous Leukocytoclastic Angiitis. Intravascular fibrin thrombi are common and may be accompanied by epidermal infarction (H&E, 400x).

Nuclear dust was previously considered to be pathoneumonic for CLA, however, several reports have shown it is also present in linear IgA bullous dermatosis, inflammatory type of epidermolysis bullosa acquisita, septic vasculitis, and dermatitis herpetiformis (LeBoit, 2005). Further, not all nuclear dust is neutrophilic in origin. Lymphocytic inflammation can also result in nuclear dust in entities such as subcutaneous panniculitis like T-cell lymphoma, Kikuchi's disease, and irritated lichenoid keratosis (LeBoit, 2005).

Direct immunofluorescence is positive in 92% of cases and can be used during all stages of lesions (Grunwald et al., 1997). Detection of immunoreactants has the highest yield when taken from lesional rather than peri-lesional skin (Barnadas et al., 2004). Deposits of fibrinogen, C3 and IgM are most frequently present, but rarely IgG and C4 can also be seen (Grunwald et al., 1997). Deposition of IgA can also be seen in conjunction with IgM or IgG, distinguishing CLA from Henoch Schonlein Purpura in which IgA deposition is found in isolation (Sais & Vidaller, 2005).

2.1.2 Urticarial vasculitis

Urticarial vasculitis (UV) is a clinicopathologic entity characterized by urticarial lesions or faint purpura persisting longer than 24 hours which on histology show a leukocytoclastic vasculitis (Aboobaker & Greaves, 1986). Patients are typically female in their fourth to fifth decade of life (Chen & Carlson, 2008). Systemic symptoms such as fever, angioedema, arthralgias, and abdominal pain are usually present (Mehregan et al., 1992). Two clinical variants, hypocomplementemia UV (HUV) and normocomplementemia UV (NUV), exist. Patients with HUV are more likely to be female and present with more severe disease along with arthralgia, glomerulonephritis, uveitis, recurrent abdominal pain, and/or obstructive lung disease (Chen & Carlson, 2008). The cause of UV is mostly unknown;, however, it can

be a manifestation of connective tissue diseases such as systemic lupus erythematosus or Sjögren's syndrome or be associated with viral infections, serum sickness, drug reactions, and exercise (Carlson & Chen, 2006).

Cutaneous findings which help to distinguish UV from chronic urticaria include burning, painful, or pruritic hive-like plaques persisting longer than 24 hours but which fade within 72 hours leaving residual areas of hypopigmentation (Carlson, 2010). Lesions tend to favor the trunk and proximal extremities (Fiorentino, 2003).

The minimal criteria required for diagnosis of UV are leukocytoclasia or fibrin deposits with or without extravasated red blood cells, features which can be subtle and overlap with the histologic findings seen in cutaneous leukocytoclastic angiitis (Black, 1999). There is a wide spectrum of histologic findings in UV, ranging from sparse neutrophilic infiltrate of small vessels to more severe lesions with a dense neutrophilic vasculitis, leukocytoclasia, extravasated red blood cells, endothelial cell swelling and fibrin deposits (Jones et al., 1983). The superficial and mid-dermal vessels are most commonly affected, however, vascular destruction can extend into the deep dermal and pannicular vessels (Davis et al., 1998; Mehregan et al., 1992). Neutrophilic vasculitis is more common in HUV whereas eosinophilic vasculitis predominates in NUV (see Figure 5) (Davis et al., 1998).

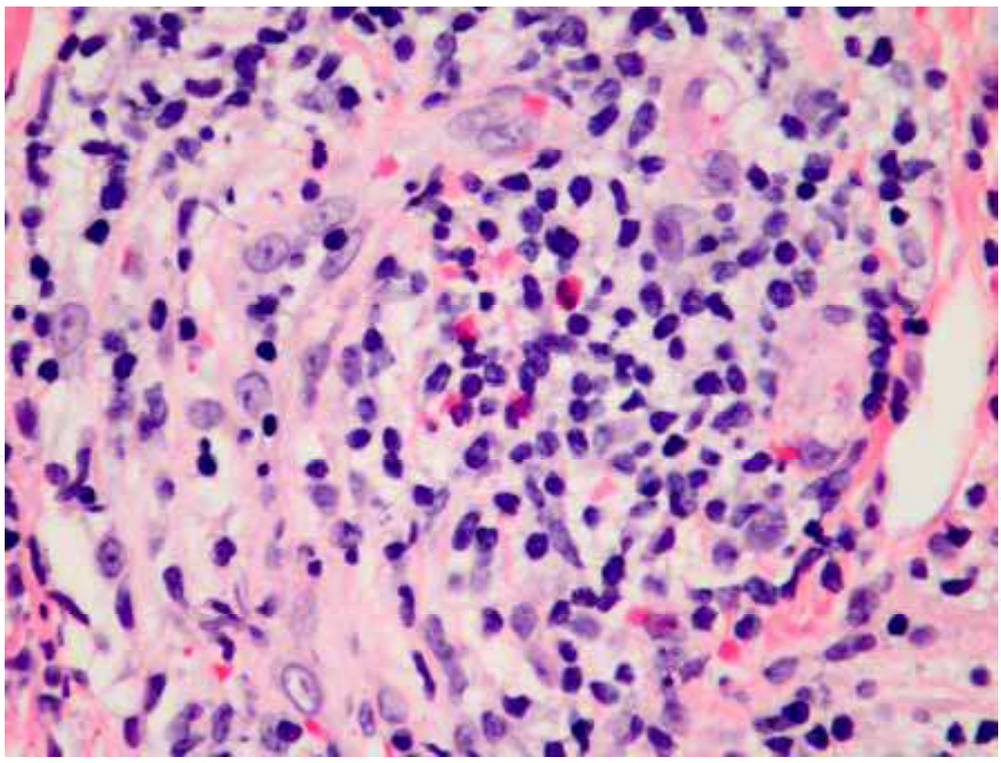


Fig. 5. Urticarial Vasculitis. A prominent eosinophilic infiltrate is present (H&E, 400x)

Direct immunofluorescence reveals peri-vascular deposits of C3 and immunoglobulins, mostly IgM, however, DIF is more frequently positive in HUV as opposed to NUV (87% versus 29%) (Mehregan et al., 1992). Likewise, basement membrane deposition of immunoglobulins and/or C3 is seen on DIF, but more commonly in HUV than NUV (70%

versus 18%) (Mehregan et al., 1992). 70% of patients with basement membrane deposition of immunoreactants will also have glomerulonephritis (Chen & Carlson, 2008).

2.1.3 Henoch schonlein purpura

Henoch Schonlein Purpura (HSP) represents approximately 10% of all cutaneous vasculitis cases and is the most common vasculitis in children, comprising about 90% of all cases (Carlson, 2010). HSP typically occurs in children aged four to eight years old with a history of upper respiratory tract infection one to two weeks prior to onset of symptoms (Fiorentino, 2003). The initial diagnosis of HSP required palpable purpura, gastrointestinal involvement, arthritis, and nephritis, however, it is now recognized that not all patients present with this tetrad of symptoms (Fiorentino, 2003). The only diagnostic criterion for HSP according to the Chapel Hill Consensus Conference (CHCC) guidelines is demonstration of IgA deposits affecting small vessels (Carlson et al., 2005). The CHCC definition is not specific for HSP, however, since IgA vascular deposits are also seen in erythema nodosum, venous stasis, cryoglobulinemia, coagulopathic vasculopathies, and livedoid vasculitis (Carlson & Chen, 2006). The diagnosis of HSP according to the American College of Rheumatology (ACR) requires two of the following: palpable purpura, age less than 20 years, abdominal pain, and/or neutrophilic vasculitis (Carlson et al., 2005). One could confuse HSP with mixed cryoglobulinemia, Wegener's granulomatosis, collagen vascular disease, hypocomplementemic vasculitis, and microscopic polyarteritis nodosa if only the more clinical ACR criteria are used for diagnosis, which does not require the demonstration of IgA deposits on direct immunofluorescence (DIF) (Magro & Crowson, 1999). Therefore, features more sensitive and specific for HSP include IgA vascular deposits and two or more of the following clinical features: age less than or equal to 20 years, abdominal pain or hematochezia, preceding upper respiratory tract infection, and/or hematuria or renal biopsy with mesangioproliferative glomerulonephritis with or without IgA deposits (Carlson, 2010).

Long term follow up of these patients is paramount as 20% of children who present with renal involvement or who have an abnormal urinalysis at the time of diagnosis will progress to chronic renal failure within 20 years (Chen & Carlson, 2008). The presence of nephrotic syndrome, hypertension, or renal failure at the outset are poor prognostic factors in children (Carlson & Chen, 2006). Adults who present with fever, rash above the waist, and an elevated erythrocyte sedimentation rate are more likely to have renal involvement (Chen & Carlson, 2008).

Cutaneous manifestations of HSP include symmetric macular erythema of the buttocks and lower extremities which progresses to palpable purpura that usually resolves within 10 to 14 days (Fiorentino, 2003).

The prototypic pathology of HSP shows a small vessel neutrophilic vasculitis indistinguishable from that seen in CLA (see Figure 6) (Carlson & Chen, 2006). At least three of the following features have been suggested as being specific for HSP: superficial plaques rather than palpable purpura, skin necrosis, retiform margins of lesions, or a livedoid pattern of hemorrhage (Piette & Stone, 1989). While the vasculitis is usually limited to the superficial and mid-dermal vessels, pandermal involvement can be seen (Magro & Crowson, 1999). A severe reaction which recapitulates a Sweet's like vascular reaction, neutrophilic interface dermatitis, dermatitis herpetiformis like abscesses, and adnexal infiltration by neutrophils can also be seen (Magro & Crowson, 1999).

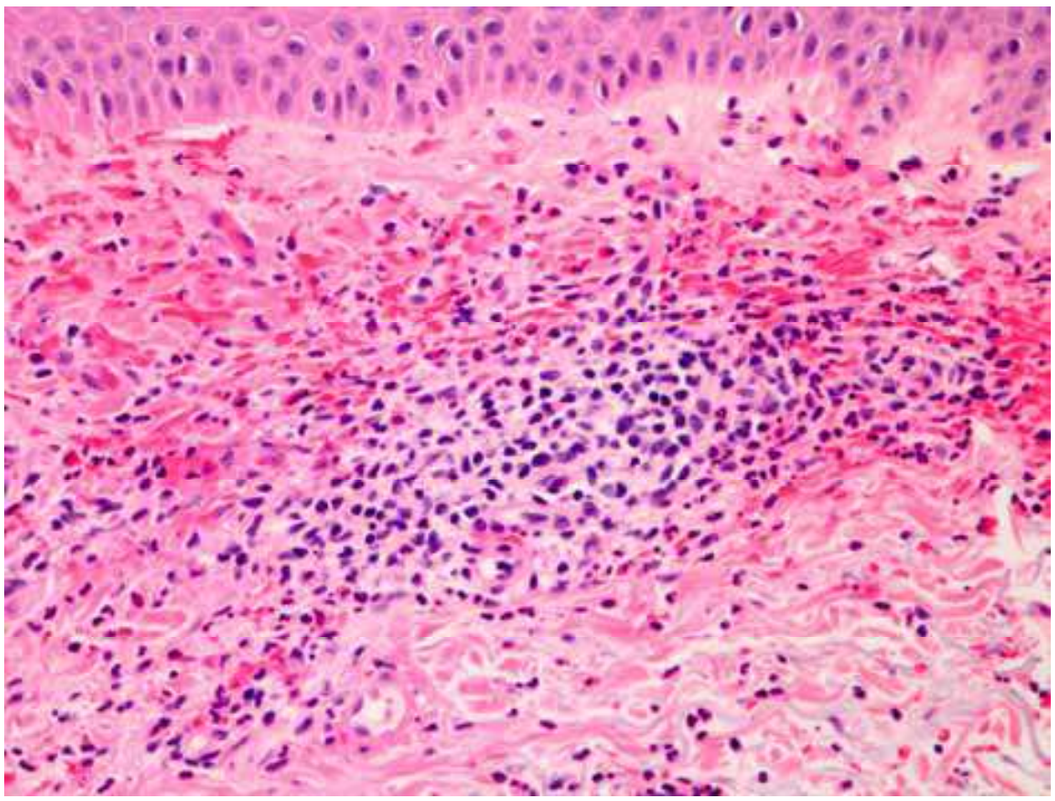


Fig. 6. Henoch Schonlein Purpura. Lesions of HSP are notable for marked red cell extravasation (H&E, 200x).

DIF reveals vascular deposits of IgA, predominately the IgA1 subclass (Egan et al., 1998). The sensitivity of DIF increases dramatically when performed on biopsies of lesions less than 48 hours in duration as compared to lesions of longer duration (85% versus 27%) (Murali et al., 2002).

Acute infantile hemorrhagic edema (AIHE) (also known as Finkelstein's Disease) is considered by some to be a variant of HSP characterized by fever, annular or targetoid skin lesions, and edema, (Carlson & Chen, 2006). Other authors consider AIHE a distinct entity from HSP owing to the fact that patients with AIHE are younger and have shorter disease courses than those patients with HSP (Karremann et al., 2009). Additionally, complications common to HSP, such as intestinal bleeding and renal involvement, are rare in AIHE (Karremann et al., 2009). Sudden onset of symptoms is seen after an upper respiratory infection, drug ingestion, or vaccination (Millard et al., 1999). The same small vessel neutrophilic vasculitis seen in HSP is also seen in AIHE, however, deposition of IgA is not a feature in AIHE (Legrain et al., 1991). Patients typically follow a benign clinical course with spontaneous resolution in 12-20 days (Millard et al., 1999).

2.1.4 Cryoglobulinemic vasculitis

Cryoglobulins are immunoglobulins which will precipitate when serum is cooled to temperatures less than 37^{o} C (Cohen et al., 1991). Cryoglobulinemia is divided into three types: Type I is composed of monoclonal immunoglobulins, type II has mixed monoclonal

and polyclonal immunoglobulins (monoclonal IgM and polyclonal IgG), and type III has only polyclonal immunoglobulins (polyclonal IgM and IgG) (Sansonno & Dammacco, 2005). Type I produces small vessel hyaline thrombi, not a true vasculitis, while types II and III result in cryoglobulinemic vasculitis (CV) (Carlson & Chen, 2006). Mixed cryoglobulinemia (types II and II) is associated with connective tissue diseases, lymphoproliferative disorders (although these are more frequently seen in association with type I), and infectious diseases (Cohen et al., 1991). Mixed cryoglobulinemia is frequently a manifestation of hepatitis C infection, although these patients less frequently present with vasculitis (Kapur et al., 2002).

The clinical triad of CV (mixed cryoglobulinemia with vasculitis) includes purpura induced by exposure to cold or prolonged standing, arthralgia, and weakness (Chen & Carlson, 2008). Non-pruritic, intermittent purpura invariably involving the lower extremities with facial and trunk sparring is always seen, however, petechiae, livedo reticularis, skin necrosis, ulcerations, and urticaria can rarely be present (Fiorentino, 2003). Other rare cutaneous presentations include polyarteritis nodosa like lesions, splinter hemorrhages, and palmar erythema (Chen & Carlson, 2008). Systemic manifestations include renal disease (presenting as hematuria, edema, or hypertension), liver disease (presenting from elevated liver enzymes and hepatomegaly to frank cirrhosis), gastrointestinal involvement (presenting as abdominal pain or gastrointestinal bleeding), lymphadenopathy, polyneuropathy, and pericarditis (Gorevic et al., 1980).

Skin biopsy of CV will demonstrate a neutrophilic vasculitis equally affecting small vessels in the papillary dermis and subcutaneous tissue (Cohen et al., 1991). Other histologic findings include endothelial swelling, extravasation of red blood cells, hyaline thrombi, and fibrinoid necrosis (Cohen et al., 1991; Gorevic et al., 1980). Rarely a lymphocytic small vessel vasculitis can be seen (Cohen et al., 1991). Direct immunofluorescence frequently reveals the presence of immunoreactants in vessel walls (typically IgG, IgM and/or C3) (Cohen et al., 1991; Gorevic et al., 1980). Deposition of immunoreactants along the basement membrane zone is not commonly seen (Gorevic et al., 1980). Hepatitis C proteins can be detected within vessel walls, even in the absence of vasculitis, and also within keratinocytes in patients with Hepatitis C virus and concurrent acute vasculitis (Sansonno & Dammacco, 2005).

2.1.5 Drug induced vasculitis

Approximately 20% of all cutaneous vasculitis eruptions result from an adverse drug reaction (Carlson, 2010). The interval between ingestion of the drug and onset of the vasculitis varies from hours to years and can commence with dosage increases or re-challenge with the agent (Carlson & Chen, 2006). The most common offenders in drug induced vasculitis include propylthiouracil, hydralazine, granulocyte-colony stimulating factor, cefaclor, minocycline, allopurinol, penicillamine, phenytoin, isotretinoin, and methotrexate (ten Holder et al., 2002).

While specific cutaneous and systemic findings vary with the offending drug (see Table 1), patients who present with limited cutaneous vasculitis in the absence of systemic involvement usually present with a maculopapular or vesicular rash over the extremities while patients with systemic vasculitis typically present with a maculopapular, vesicular, or purpuric rash which is not limited to the extremities (Mullick et al., 1979).

	Systemic Organs Involved	**Cutaneous Findings**	**Duration of Therapy before Onset of Symptoms**
Propylthiouracil	Renal (focal segmental glomerulosclerosis, mesangial proliferation), Pulmonary (hemoptysis, wheezing, congestion, cough, dyspnea), Musculoskeletal (myositis, cramping, elevated creatine kinase), Ear (decreased hearing, bilateral deafness, tinnitus)	Purpuric lesions progressing to necrotic ulcers	3 days-7 years
Hydralazine	Renal (pauci-immune glomerulonephritis), Pulmonary, Musculoskeletal (arthralgias, myalgias)	Palpable purpura, maculopapular eruptions on the lower extremities and hemorrhagic blisters on the legs, arms, trunk, nasal septum, and uvula	6 months-13 years
Granulocyte Colony Stimulating Factor	Systemic symptoms less common; Renal (vasculitis), Musculoskeletal (arthralgias)	Subcutaneous nodules, purpura, hemorrhagic bullae, erythematous macules	Days to Weeks
Allopurinol	Always presents with systemic symptoms; Renal (glomerulonephritis), Hepatic (elevated liver enzymes, granulomatous infiltration), Musculoskeletal (myalgias), Other (lymphadenopathy, seizures)	Macular rash more prominent on the back and abdomen, non-follicular macular exanthem on trunk and proximal extremities, erythema multiforme	2 hours-9 years
Cefaclor	Renal and Musculoskeletal	Serum sickness like reaction limited to the face and extremities	1-2 weeks
Minocycline	Renal (elevated creatinine), Hepatic (elevated liver enzymes), Ocular (conjunctivitis, swelling of the eye), Musculoskeletal (arthralgias, polyarthritis)	Urticarial eruption, erythema nodosum, non-palpable purpura, livedo reticularis, erythematous macular eruptions	9 days-9 months
Penicillamine	Renal (glomerulonephritis), Pulmonary (coughing, hemoptysis, lung infiltrates)	Cutaneous ulcers on hands and ears, purpuric rash	2 months-18 years
Phenytoin	High mortality rate; vasculitis involving the kidney, liver, spleen, and lung	Pruritic maculopapular rash	1 week-17 years
Isotretinoin	Renal (glomerulonephritis), Pulmonary (Wegener's granulomatosis), Musculoskeletal (myalgias, arthralgias)	Pruritic papules	6-16 weeks
Methotrexate	Fever	Erythematous palpable purpura	1-5 days

Adapted from ten Holder et al., 2002

Table 1. Drugs Most Frequently Associated with Vasculitis

Numerous cases report positive ANCA following ingestion of certain drugs. The drugs most commonly associated with ANCA positive vasculitis are propylthiouracil and hydralazine. Methimazole, phenytoin, thiazide, minocycline, allopurinol, penicillamine, sulfasalazine, cephotaxime, and retinoids have also been implicated (Cuellar, 2002). Cutaneous findings in patients with drug induced ANCA associated vasculitis include acral purpuric plaques and nodules, most commonly found on the extremities, face, breast, and ears (Fiorentino, 2003). Systemic involvement is more common in the ANCA associated drug induced vasculitides (Chen & Carlson, 2008).

Other drugs can cause a vasculitis which clinically and histologically resembles urticarial vasculitis (appetite suppressants, methotrexate, procainamide, fluoxetine), Churg Strauss syndrome (leukotriene inhibitors, macrolides), Henoch-Schonlein purpura (propylthiouracil, levodopa, carbidopa), and Wegener's granulomatosis (propylthiouracil) (Cuellar, 2002).

Skin biopsy usually reveals a leukocytoclastic vasculitis (LCV) similar to that seen in other small vessel vasculitis syndromes characterized by vascular and interstitial neutrophilic infiltration, leukocytoclasis, endothelial cell swelling, fibrinoid necrosis, and extravasation of red blood cells (Bahrami et al., 2006). Determining a drug induced versus non-drug induced etiology is a diagnostic dilemma for clinicians and pathologists. Tissue eosinophilia can be present in drug induced LCV, however, its existence does not exclude other non-drug induced etiologies such as arthropod assault, which will also show prominent interstitial eosinophils (Bahrami et al., 2006). One study suggested the presence of vascular fibrin deposition should exclude a drug related LCV, however, later studies have failed to replicate this findings (Bahrami et al., 2006; Mullick et al., 1979). Intravascular fibrin thrombi and epidermal changes including vesicle formation can occasionally be seen (Bahrami et al., 2006).

Recent attention has been given to vasculitis secondary to cocaine adulterated with levamisole. Patients present clinically with retiform purpura and skin biopsy shows a leukocytoclastic vasculitis with thrombosis (Walsh et al., 2010). Mural fibrin, extravasated red blood cells, nuclear dust, and luminal thrombosis can also be seen (see Figure 7) (Waller et al., 2010). A diagnostic pit fall for clinicians and dermatopathologists is "cocaine-induced pseudovasculitis" in which the clinical and serologic findings are suggestive of vasculitis, but the histopathologic findings of vasculitis are absent (Friedman & Wolfsthal, 2005). These patients can also present with retiform purpura and skin biopsy shows fibrin thrombi occluding small superficial and deep dermal vessels without evidence of vasculitis (Waller et al., 2010).

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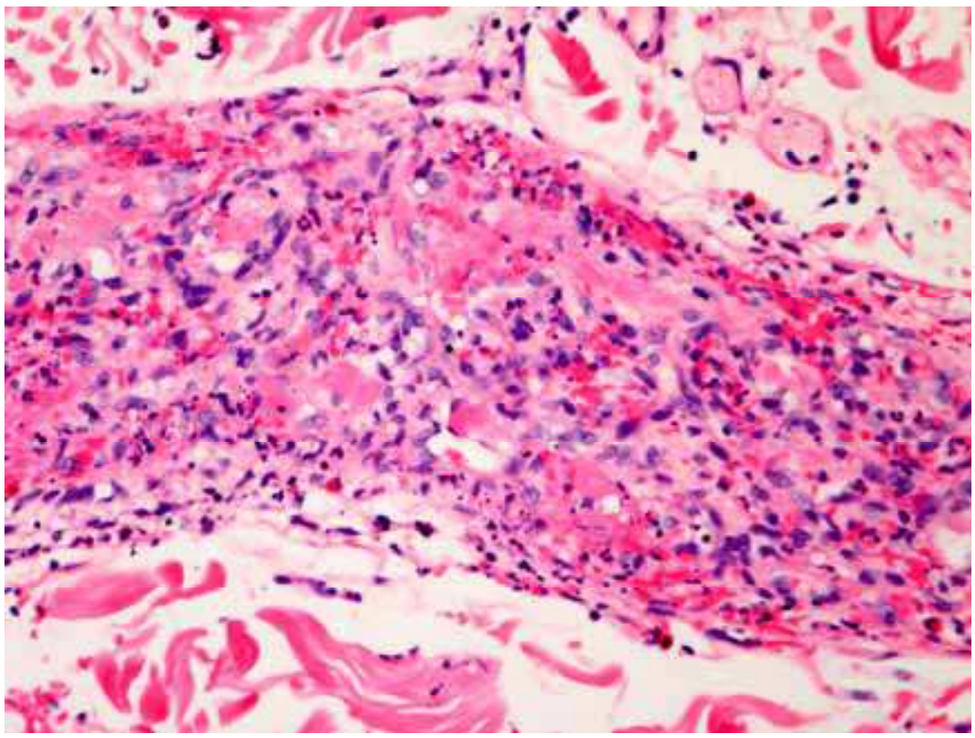


Fig. 7. Levamisole-Induced Vasculitis. Complete effacement of the vessel wall with extensive fibrin thrombosis and neutrophilic infiltrates reminiscent of an infectious etiology (H&E, 200x).

2.1.6 Connective tissue disease associated vasculitis

Connective tissue disease (CTD) vasculitis is an uncommon complication most frequently seen in patients with systemic erythematosus (SLE), rheumatoid arthritis (RA), and Sjögren's syndrome (SS) but can also rarely be seen in dermatomyositis, scleroderma, and polychondritis (Carlson & Chen, 2006). The usual presentation is arterial and capillary involvement represented clinically by purpura, vesiculobullous lesions, urticaria, and splinter hemorrhages (Carlson, 2010). Ulcers, subcutaneous nodules, gangrene, livedo racemosa, and pyoderma gangrenosum can also be seen and represent arterial involvement (Carlson, 2010).

Skin biopsy typically reveals a vasculitis of small vessels, although medium sized vessel involvement can occasionally be seen (see Figure 8) (Carlson, 2010). The findings of both small and medium sized vessel vasculitis in the same biopsy are characteristic of CTD vasculitis (Chen & Carlson, 2008). Patients with CTD vasculitis can show p-ANCA or, more rarely, c-ANCA on indirect immunofluorescence (Carlson & Chen, 2006). Serology for anti-proteinase 3 and anti-myeloperoxidase is typically negative in these patients, ruling out Wegener's granulomatosis and Churg Strauss syndrome, respectively (Merkel et al., 1997). While the histologic features of CTD vasculitis are similar despite the etiology, certain extravascular findings may help aid in distinguishing which specific CTD is present. Interface dermatitis with increased dermal mucin is seen in SLE and dermatomyositis; dermal sclerosis is seen in scleroderma; granulomatous dermatitis is seen in RA and SLE; and interstitial neutrophilia is seen in SLE and SS (Chen & Carlson, 2008). Chronic

lymphocytic vasculitis is the suspected etiology for endarteritis obliterans, a vasculopathy characterized by progressive blood vessel occlusion with subsequent internal organ ischemia seen in patients with CTD vasculitis (Carlson & Chen, 2006).

2.1.7 Rheumatoid vasculitis

Rheumatoid vasculitis (RV) is an uncommon complication of rheumatoid arthritis (RA) with significant mortality (Chen et al., 2002). RV is associated with high rheumatoid factor titer, joint erosions, extra-articular symptoms, rheumatoid nodules, male gender, increasing number of treatment with disease modifying agents, and prior treatment with D-penicillamine or azathioprine (Sayah & English, 2005). Onset is typically 10-14 years after the onset of RA (Sayah & English, 2005). Diagnosis of RV requires RA plus one or more of the following: mononeuritis multiplex, acute peripheral neuropathy, peripheral gangrene, acute necrotizing vasculitis seen on biopsy plus systemic symptoms, or deep cutaneous ulcers or extra-articular disease if associated with infarcts or vasculitis (Sayah & English, 2005). Cutaneous findings are the most common extra-articular manifestation in RV and can be seen in 80-89% of all patients and are frequently the presenting symptom (Chen et al., 2002). Patients with cutaneous RV generally have a good prognosis while those with RV involving nerves or bowel typically have a fatal outcome (Carlson & Chen, 2006).

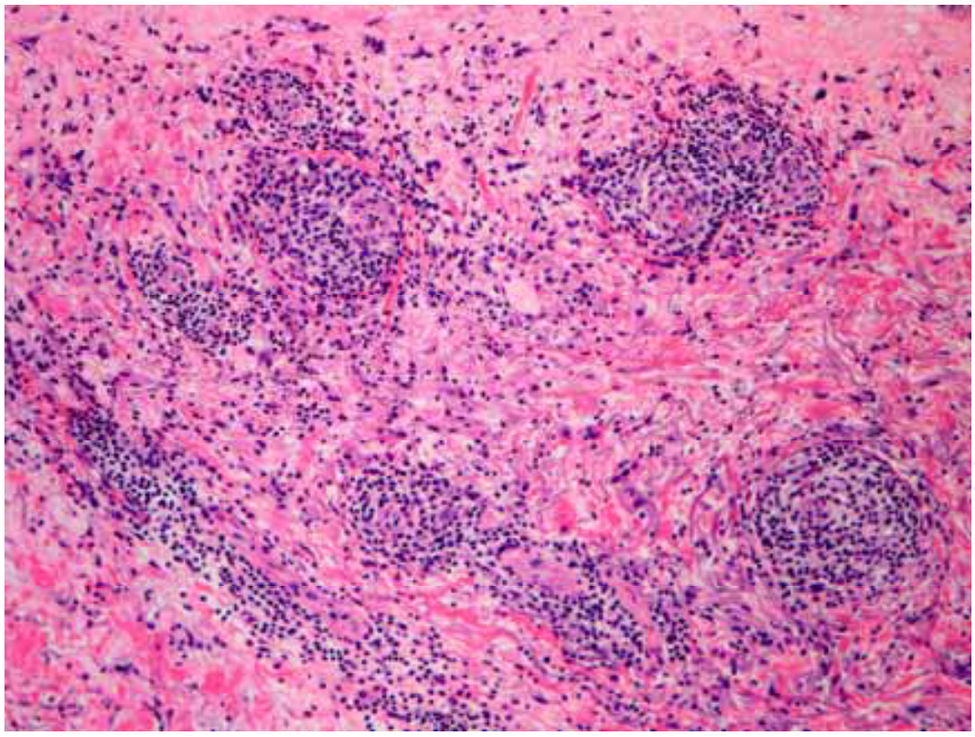


Fig. 8. Lymphocytic Vasculitis. Connective tissue disease may present with a predominately lymphocytic infiltrate (H&E, 100x).

Palpable purpura on the lower extremities is the most common cutaneous presentation (Genta et al., 2006). Other manifestations include ulcers, maculopapular erythema, hemorrhagic blisters, erythema elevatum diutinum, livedo reticularis, subcutaneous

nodules, and atrophie blanche (Chen et al., 2002). Ulcers tend to be found on the dorsum of the foot or upper calf, locations which are different from ulcerations due to atherosclerosis and diabetes, a finding which may help clinically distinguish these entities (Genta et al., 2006). Small, brown, painless infarcts of the nail fold or edge, also known as Bywaters lesions, are characteristic of RV (Sayah & English, 2005).

Histologic diagnosis of RV is complicated by the fact that vessels ranging from subcutaneous muscular arteries to venules can be involved and vessels in all stages of acute and healing vasculitis can be identified in the same specimen (Chen et al., 2002). Three histologic patterns of vasculitis may be seen. A necrotizing leukocytoclastic vasculitis of dermal venules is seen in patients with palpable purpura, hemorrhagic bullae, maculopapular erythema, and erythema elevatum diutinum (Chen et al., 2002). An acute or healing arteritis of the dermal-subcutaneous vessels similar to that seen in polyarteritis nodosa is seen in patients with subcutaneous nodules, livedo reticularis, and ulcers (Carlson & Chen, 2006). The last pattern is a mixed venulitis and arteritis and is seen in patients with subcutaneous nodules, atrophie blanche, and palpable purpura (Chen et al., 2002). Other histologic patterns that can be seen include folliculocentric neutrophilic vasculitis, pustular vasculitis with epidermal microabscess formation resembling dermatitis herpetiformis, and granulomatous vasculitis composed namely of lymphocytes and histiocytes (Magro & Crowson, 2003). Small vessel occlusive arteritis is seen in Bywaters lesions (Sayah & English, 2005). Vascular deposition of immunoglobulin, typically IgM, can frequently be seen on direct immunofluorescence and is associated with the presence of extra-articular manifestations (Rapoport et al., 1980).

2.1.8 Lupus vasculitis

Lupus vasculitis (LV) can be seen in 19-36% of patients with systemic lupus erythematosus (SLE) and 7-12% of patients with subacute cutaneous lupus erythematous (SCLE) (Carlson & Chen, 2006). Patients with LV are more frequently younger, male patients when compared to SLE patients without vasculitis (Carlson & Chen, 2006). Laboratory abnormalities include anemia, an elevated erythrocyte sedimentation rate and anti-La/SS-B antibodies, which are more common in patients with LV than those with non-vasculitis SLE (Chen & Carlson, 2008). Systemic LV, with or without cutaneous LV, is associated with a higher rate of mortality (Carlson & Chen, 2006).

The most common cutaneous findings are small painful macules or depressed punctuate scars over the palmar surfaces and finger tips which represent palmar and digital infarcts (Carlson & Chen, 2006). Other manifestations include palpable purpura, urticaria, and livedo reticularis of the lower extremities (Fiorentino, 2003).

Neutrophilic vasculitis of small vessels is the most frequent histological findings on skin biopsy (Drenkard et al., 1997). Neutrophilic or lymphocytic vasculitis involving medium sized muscular vessels can also be seen (Carlson & Chen, 2006). Biopsies of punctuate palmar lesions or areas of livedo reticularis show typical findings of livedoid vasculitis such as thickening and hyalinization of dermal and subcutaneous small and muscular vessels, inconspicuous lymphocytic perivascular infiltration, endothelial swelling, occlusion of the vessel lumen by fibrin, and endothelial necrosis can also be seen (Yasue, 1986). Livedoid vasculitis is associated with an increased risk of developing SLE involving the central nervous system (Yasue, 1986). Concomitant findings of cutaneous lupus

erythematosus and LV can be seen within the same biopsy (Carlson & Chen, 2006). Direct immunofluorescence will reveal vascular deposition of IgG, IgM, or complement in approximately 55% of cases and co-existing basement membrane zone deposition of immunoglobulins (mostly IgM but rarely IgG) and complement in 60% of cases (Yasue, 1986).

2.1.9 Sjögren's syndrome

Sjögren's syndrome (SS) is an autoimmune disease primarily affecting exocrine glands leading to dry mouth and dry eyes (Ramos-Casals et al., 2004). Patients with SS vasculitis are more likely to have systemic involvement of their disease such as arthritis, peripheral neuropathy, central nervous system vasculitis, Raynaud's phenomenon, and renal disease (Carlson & Chen, 2006). Presence of antinuclear antibodies, anti-Ro/SS-A antibodies, rheumatoid factor, and cryoglobulins are frequent laboratory findings (Carlson & Chen, 2006).

The most common cutaneous findings are urticaria, palpable purpura, and ecchymoses (Fiorentino, 2003). Erythema multiforme, erythema perstans, and erythema nodosum can also be seen (Alexander & Provost, 1987).

Two distinct histologic patterns are seen. A neutrophilic vasculitis with extravasation of red blood cells, fibrin deposition, and nuclear dust is seen in patients with antinuclear antibodies, high titers of anti-Ro/SS-A and anti-La/SS-B antibodies, hypergammaglobulinemia, hypocomplementemia, and positive rheumatoid factor (Alexander & Provost, 1987). A lymphocytic vasculitis with fibrinoid necrosis is associated with negative antinuclear antibodies, low titers of anti-RO/SS-A and anti-La/SS-B antibodies, normocomplementemia, and normal globulin levels (Alexander & Provost, 1987). Necrotizing vasculitis of medium sized vessels can occasionally be seen (Ramos-Casals et al., 2004).

2.1.10 Erythema elevatum diutinum

Erythema elevatum diutinum (EED) is a chronic relapsing and remitting cutaneous vasculitis occurring in middle aged patients (Wahl et al., 2005). While the etiology is largely unknown, there is an association between EED and connective tissue disease, infectious agents (hepatitis, syphilis, HIV, and Streptococcus), and hematological abnormalities (myelodysplasia, multiple myeloma, and lymphoma) (Wahl et al., 2005). ANCA can occasionally be detected in patients with EED (Carlson & Chen, 2006). Lesions are typically symmetric, tender, red or brown papules, plaques, or nodules on the extensor surfaces of the extremities (Yiannias et al., 1992).

Skin biopsy of early lesions reveals a leukocytoclastic vasculitis of small vessels in which neutrophils are the predominant inflammatory cell (see Figure 9) (Yiannias et al., 1992). The dermis is relatively cellular with fibroblasts, histiocytes, and neutrophils predominating with relatively sparring of the epidermis and papillary dermis (Wahl et al., 2005). Older lesions show predominately fibrosis and granulation tissue with some lesions showing xanthomatization of the mid-dermis (Yiannias et al., 1992). Dense areas of laminated fibrosis contributes to the nodular appearance seen clinically (LeBoit & Cockerell, 1993). Direct immunofluorescence is generally non-diagnostic, but vascular deposition of IgG, IgM, complement (C3), and fibrinogen can be seen (Yiannias et al., 1992).

2.1.11 Granuloma faciale

Granuloma faciale (GF) usually presents in middle aged adults as red-brown plaques, nodules, or papules which usually arise on the face (Ortonne et al., 2005). Clinically, these lesions can be mistaken for sarcoidosis, lymphoma, discoid lupus erythematosus, and basal cell carcinoma (Carlson & Chen, 2006).

Skin biopsy shows a leukocytoclastic vasculitis within in the upper and reticular dermis and rarely involves the hypodermis (Marcoval et al., 2004). The dermis densely infiltrated by inflammatory cells, predominately eosinophils and plasma cells, distinguishing this entity from erythema elevatum diutinum, where neutrophils predominate (see Figure 10) (LeBoit, 2002). The cellular dermis is separated from the unremarkable epidermis by a grenz zone (see Figure 11) (Ortonne et al., 2005). Fibrinoid necrosis, extravasated red blood cells, and hemosiderin deposition can also be seen (Marcoval et al., 2004). Concentric perivascular fibrosis can be seen in older lesions (LeBoit, 2002). Perivascular and basement membrane deposition of immunoglobulins (mostly IgG but also IgA and IgM), complement (C3), and fibrinogen can be seen on direct immunofluorescence (Barnadas et al., 2005).

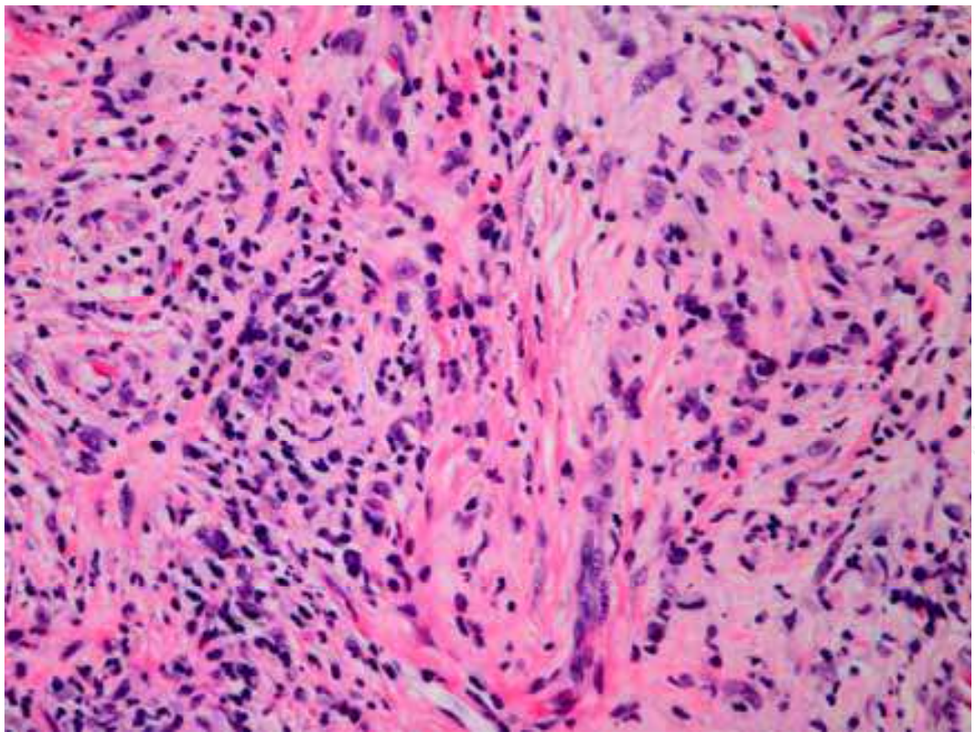


Fig. 9. Erythema Elevatum Diutinum. Older lesions are characterized by dermal sclerosis and scarring (H&E, 100x).

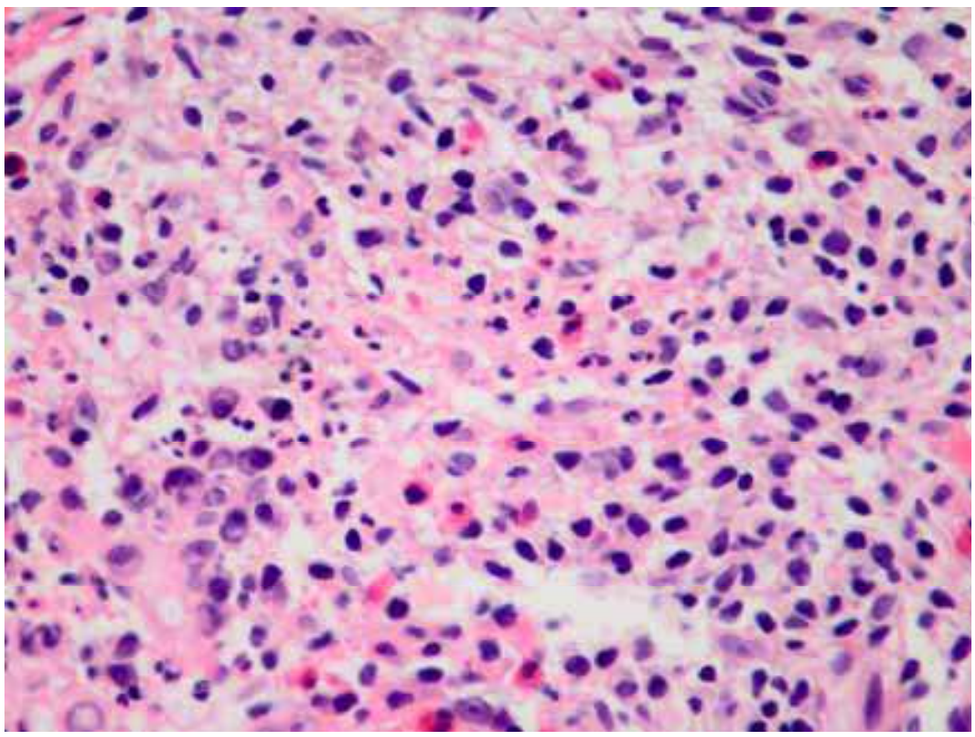


Fig. 10. Granuloma Faciale. Numerous eosinophils are present in the mixed dermal infiltrate (H&E, 400x)

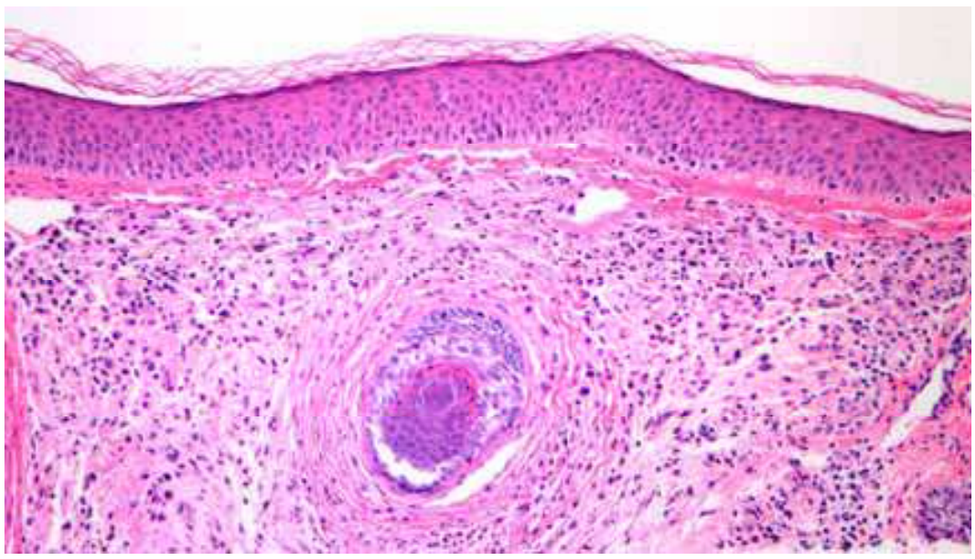


Fig. 11. Granuloma Faciale. A dense inflammatory infiltrate fills the dermis underneath a prominent Grenz zone (H&E, 100x).

2.2 Non-immune complex mediated vasculitis in small muscular arteries and arterioles

2.2.1 Churg strauss syndrome

Churg Strauss Syndrome (CSS) is a clinically distinct entity characterized by asthma (usually adult onset), allergic symptoms (ex. allergic rhinitis), peripheral and tissue eosinophilia, and systemic vasculitis affecting small to medium sized vessels (Chen & Carlson, 2008). The classic presentation follows three phases, the prodromal phase which consists of atopic disease, namely asthma or allergic rhinitis followed by the second phase consisting of peripheral and tissue eosinophilia and finally the third phase which is heralded by a life threatening systemic vasculitis (Lanham et al., 1984). Cutaneous lesions accompanied by peripheral neuropathy are the most common clinical symptoms (Chen et al., 2007). Other clinical findings include pulmonary infiltrates, abdominal pain, intestinal obstruction leading to perforation (secondary to obstructive submucosal eosinophilic infiltrates), pericarditis, congestive heart failure, neuropathy, joint pain, and myalgia (Lanham et al., 1984). Renal involvement in the form of focal segmental glomerulonephritis is rarely seen (Lanham et al., 1984). The renal findings in CSS and Wegener's granulomatosis are indistinguishable; however, renal involvement in CSS is extraordinarily rare and follows a benign course whereas renal disease is common in Wegener's granulomatosis and frequently leads to renal failure (Lanham et al., 1984).

Laboratory findings typically include eosinophilia and elevated IgE; approximately two thirds of patients will have a positive ANCA, usually p-ANCA (Frankel et al., 2002). Patients with a positive p-ANCA are more likely to have vasculitis and renal and central nervous system involvement (Choi et al., 2008). Vaccination, leukotriene inhibitors, and withdraw of corticosteroids have all been implicated as possible factors precipitating the onset of symptoms (Fiorentino, 2003).

Three main types of cutaneous lesions are seen: erythematous maculopapules, hemorrhagic lesions (ranging from petechiae to ecchymosis) associated with necrosis and ulceration, and tender, deep seated nodules on the scalp and temple (Choi et al., 2008). Other cutaneous manifestations include livedo reticularis, wheals, vesicles, and bullae (Chen et al., 2007).

Skin biopsy reveals three major histologic features: eosinophilic and neutrophilic vasculitis of small to medium sized vessels in the superficial and mid-dermal vessels ranging from a mild perivascular cuffing of inflammatory cells to a necrotizing arteritis which can recapitulate polyarteritis nodosa (PAN); interstitial dermal infiltration with eosinophils; or granulomas (see Figure 12) (Carlson & Chen, 2006; Lanham et al., 1984). All three histologic patterns may be seen in the same biopsy (Lanham et al., 1984). While the vasculitis typically involves small vessels, medium sized vasculitis can also occasionally be seen (Lanham et al., 1984). Lesions in the healing stages will show fibrosis with calcified nodules and a sparse or complete absence of inflammatory cells (Carlson & Chen, 2006; Chen et al., 2007). This is in contrast to PAN where the acute stage is marked by neutrophils and the healing stage by lymphocytes and histiocytes (Chen et al., 2007).

Two types of extravascular granulomas exist. The "blue" granulomas show palisading histiocytes surrounding basophilic degenerated collagen bundles (Chen et al., 2007). "Red" granulomas are also characterized by palisading histiocytes which surround a central zone of eosinophilic debris and collagen bundles (Carlson, 2010). While granulomatous arteritis may be found within internal organs of patients with CSS, the initial series report by Churg and Strauss only demonstrated perivascular or extravascular granulomas within skin

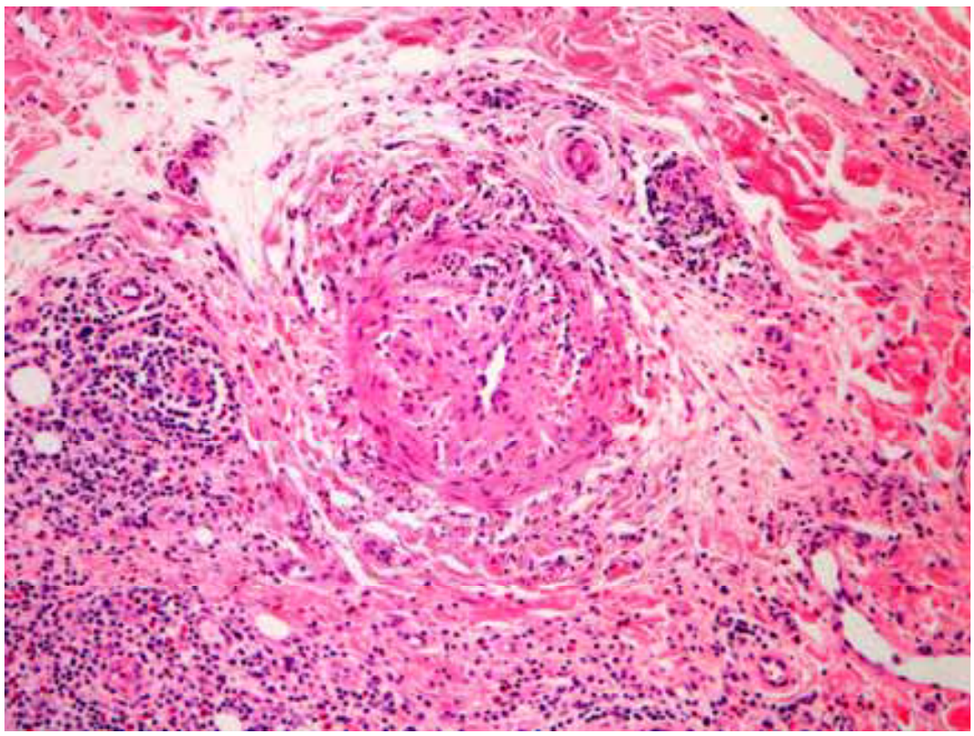


Fig. 12. Churg-Strauss Syndrome. Medium-sized vessel vasculitis with a prominent eosinophilic infiltrate (H&E. 100x).

lesions (Churg & Strauss, 1951). Granulomatous arteritis is a relatively rare findings in CSS. Chen et al recently suggested five scenarios which may contribute to the infrequency of this finding: biopsy was not performed over areas of livedo reticularis; biopsy did not extend into the subcutis; serial sections on the specimen were not performed; biopsy was taken after the start of treatment; or biopsy was not taken during the granulomatous stage (Chen et al., 2007). Direct immunofluorescence is typically negative giving rise to the name "pauci-immune" vasculitis (Carlson, 2010).

2.2.2 Wegener's granulomatosis

The initial description of Wegener's granulomatosis (WG) included three clinical findings: necrotizing granulomas with a predilection for the upper and lower airways, systemic small vessel vasculitis, and pauci-immune glomerulonephritis (Fiorentino, 2003). The most common initial presentation involves the upper and lower airways, with renal development occurring later (Frankel et al., 2002). Since all three clinical features are only concurrently present in 16% of patients, other criteria are used to establish the diagnosis (Carlson & Chen, 2006). The Chapel Hill Consensus Conference (CHCC) defined WG as necrotizing vasculitis of the small to medium size vessels and granulomatous inflammation of the respiratory tract (Jennette et al., 1994). The documentation of granulomas does not necessarily require histology, but can rather be made using non-invasive techniques such as radiology (Jennette et al., 1994). The CHCC recognized, however, that the broad definition they used to classify WG left significant overlap between WG and microscopic polyangiitis (Jennette et al., 1994). The American College of Rheumatology (ACR) criteria for diagnosis requires two or more of

the following: nasal or oral inflammation, chest x-ray showing nodules, infiltrates, or cavities, microscopic hematuria, and/or granulomatous inflammation on biopsy (Carlson et al., 2005). The positive predictive value of the ACR criteria for diagnosing WG ranges from 25-40% (Rae et al., 1998). Typical laboratory findings include a positive C-ANCA in 75-80% of patients (Fiorentino, 2003). WG is highly fatal, with a one year mortality rate of greater than 80% in untreated patients (Chen & Carlson, 2008). Relapse within 5 years occurs in 50% of patients (Carlson & Chen, 2006).

A limited form of WG which typically involves younger patients is characterized by no or minimal renal dysfunction, limited pulmonary involvement, and no critical organ involvement (i.e., gastrointestinal, ocular, or central nervous system) exists (Carlson & Chen, 2006). The cutaneous presentation is usually limited to purpura or ulcers (Carlson & Chen, 2006).

Cutaneous lesions are found in 50% of patients but may be the presenting symptoms in up to 10% of cases (Chen & Carlson, 2008). Cutaneous manifestations fall into three categories: palpable or non-palpable purpura which reflects a small vessel vasculitis; ulcers or digital infarcts secondary to small to medium sized vessel vasculitis; or polymorphic lesions including rheumatoid like nodules over the extensor surfaces, urticaria, vesiculobullous lesions, gingival hyperplasia, or ulcers like those seen in pyoderma gangrenosum, resulting from extravascular granulomas (Carlson, 2010). Other dermatological manifestations include petechiae, bullae, and erythema (Daoud et al., 1994). Mucosal ulcerations, xanthomas, and livedo reticularis can also be seen (Francès et al., 1994). A larger, suppurative ulceration involving the entire orbit and zygoma has been reported in a patient with limited WG (Bull et al., 1993). Hemorrhagic bullous plaques and erythematous pustules reminiscent of Sweet's syndrome have been described (Gürses et al., 2000).

Four histological patterns can be seen on skin biopsies: (1) Leukocytoclastic vasculitis (LCV) characterized by necrotizing, neutrophilic vasculitis of small to medium sized dermal blood vessels; (2) Palisading granulomas with a central core of basophilic collagen surrounded by histiocytes and neutrophils reminiscent of granulomas seen in Churg-Strauss syndrome; (3) Granulomatous vasculitis with perivascular and periadnexal lymphohistiocytic granulomatous infiltrate and giant cells within the walls of muscular vessels of the subcutis; and (4) Perivascular and periadnexal infiltration of granulomas composed of large, atypical lymphocytes (see Figure 13) (Hu et al., 1977). Other non-specific histological findings include fibrin deposition within the lumen of and surrounding blood vessels, extravasation of red blood cells, endothelial cell swelling, and nuclear debris (Barksdale et al., 1995). Histological findings in patients with WG but without cutaneous vasculitis include foreign body giant cell reaction, fibrosis, hemorrhage, pseudoepitheliomatous hyperplasia, and interstitial eosinophilia (Carlson & Chen, 2006). Epidermal changes are rarely seen and include bulla formation and epidermal necrosis (Daoud et al., 1994). Biopsies of cutaneous lesions from patients with limited WG will often show granulomatous dermatitis but will seldom show vasculitis (Carlson & Chen, 2006).

Patients presenting with necrotizing vasculitis or granulomas composed of lymphocytes have a higher mortality rate than those presenting with palisading granulomas or granulomatous vasculitis (Hu et al., 1977). The cutaneous pathology correlates with the presence of systemic disease, specifically with respect to articular and renal involvement (Francès et al., 1994). Patients presenting with LCV are more likely to have concurrent

musculoskeletal and renal involvement and a more rapidly progressive disease course when compared to patients without cutaneous manifestations and are more likely to, over time, develop renal, musculoskeletal, and ocular manifestations when compared to patients with granulomatous dermatitis (Barksdale et al., 1995).

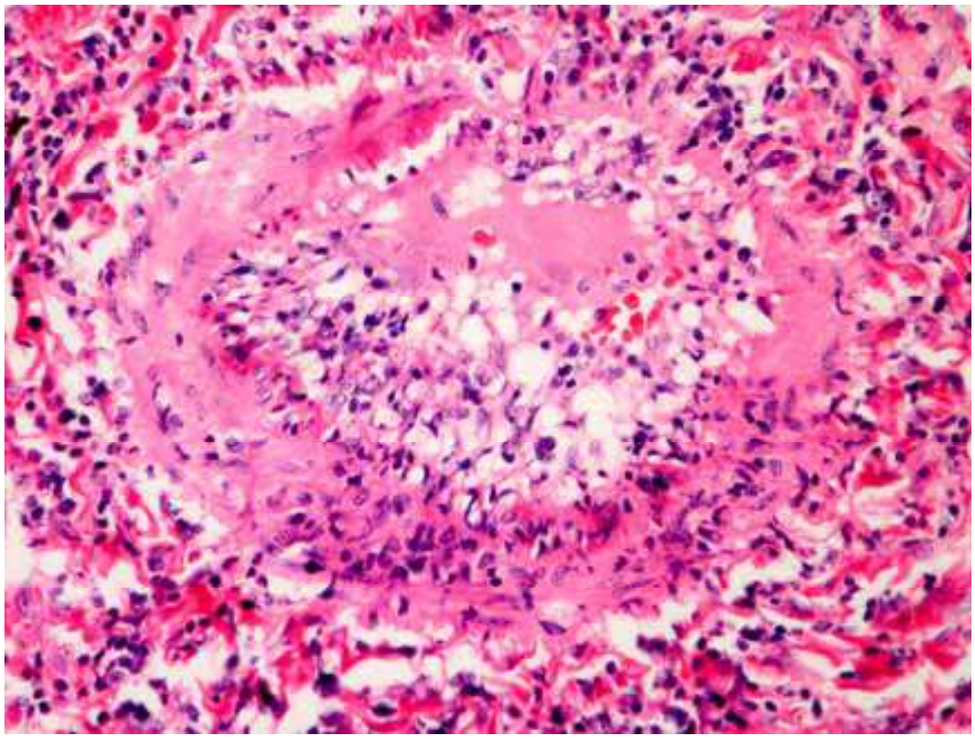


Fig. 13. Wegener's Granulomatosis. Granulomatous and necrotizing vasculitis can be seen in this section of pulmonary artery (H&E, 200x).

While direct immunofluorescence typically fails to demonstrate immunoglobulin or complement deposition on renal biopsies, skin biopsies frequently show perivascular deposits of IgG, IgM, IgA, and C3 in subepidermal and dermal vessels (Brons et al., 2001). In patients who have had a relapse of WG, immunoglobulin deposits can be seen along the basement membrane and within the dermis (Brons et al., 2001).

2.2.3 Microscopic polyangiitis (microscopic polyarteritis)

Microscopic polyangiitis (MPA) is a systemic neutrophilic vasculitis of small vessels (Carlson, 2010). Men are slightly more affected then women and the average age of onset is 50 years (Guillevin et al., 1999). The major systemic finding includes rapidly progressive focal segmental necrotizing glomerulonephritis; pulmonary hemorrhage, skin involvement, and antibodies to p-ANCA are also frequently present (Frankel et al., 2002). A prodromal phase consisting of weight loss, fatigue, fevers, arthralgias, and myalgias is often present months to years before the acute onset of the disease (Fiorentino, 2003). Drugs (specifically antibiotics), hepatitis B, streptococcal infection, and neoplasia have all been implicated as inciting factors in MPA (Savage et al., 1985). The overall mortality rate for MPA is 32%, similar to polyarteritis nodosa (PAN), Wegener's granulomatosis (WG), and Churg-Strauss

syndrome (CSS), however, relapses are more frequent in MPA than seen in the other vasculitis syndromes (Guillevin et al., 1999). Since the histologic features of MPA are similar and in some instances indistinguishable from WG and CSS, the following criteria have been suggested for diagnosis: 1) no evidence of granulomatous inflammation (either by histology or radiology), 2) neutrophilic vasculitis of small vessels and/or glomerulonephritis without immune complex deposition, and 3) involvement of two or more organ systems as documented by biopsy or other laboratory or radiological markers (i.e., proteinuria, hematuria) (Chen & Carlson, 2008).

Up to 15% of patients with MPA will present with skin disease and 65% or less will develop skin disease throughout the course of their illness (Carlson & Chen, 2006). The most common cutaneous presentation is palpable purpura and petechiae (Seishima et al., 2004). Other manifestations include splinter hemorrhages, nodules, palmar erythema, livedo, urticaria, hemorrhagic bullae, infarcts, facial edema, annular purpura, ulcers, and telangiectases (Carlson & Chen, 2006). One case of MPA reported in a patient with palpable purpura, myalgias, anorexia, and synovitis but no evidence of pulmonary or renal involvement suggests that a cutaneous limited variant of MPA may exist (Irvine et al., 1997).

While a wide spectrum of pathologic changes can be seen, the classic histologic features of MPA on skin biopsy include a neutrophilic vasculitis of small vessels in the upper to mid-dermis and subcutis (Carlson & Chen, 2006). Rarely medium sized vessels can be involved (Lhote et al., 1998). Other findings on the histologic continuum of MPA include lymphocytic perivascular infiltration in the upper dermis, mixed lymphocytic and neutrophilic perivascular infiltration in the mid to deep dermis, and mixed lymphocytic and histiocytic perivascular infiltration in the mid dermis (Seishima et al., 2004). Other non-specific findings of leukocytoclastic vasculitis similar to those seen in cutaneous leukocytoclastic angiitis (CLA) include fibrinoid necrosis and leukocytoclasis (Homas et al., 1992). The clinical appearance of livedo racemosa presents histologically as a vasculitis affecting deep dermal and subcutaneous vessels and a deep incisional biopsy is indicated in these patients to ensure that the subcutis is sampled (Nagai et al., 2009). Rarely patients can present with oral ulcerations which will also reveal a small vessel vasculitis on histologic examination (Savage et al., 1985). A unique histologic finding in MPA is the presence of active vasculitis, healed vessels, and unaffected vessels in the same tissue biopsy (Lhote et al., 1998).

Small vessel vasculitis is diagnostic of MPA and excludes the diagnosis of PAN, even if medium sized vessels are involved (Lhote et al., 1998). Further, vascular nephropathy is the common renal finding in PAN whereas MPA is characterized by rapidly progressive focal segmental necrotizing glomerulonephritis (Lhote et al., 1998). WG is another small vessel vasculitis similar to MPA, however, granulomatous inflammation characteristic of WG is absent in MPA (Lhote et al., 1998). Absence of immunoglobulin deposition on direct immunofluorescence distinguishes MPA from CLA (Carlson & Chen, 2006).

2.2.4 Septic vasculitis

Approximately 22% of all cases of cutaneous vasculitis are associated with an infectious etiology (viruses, bacteria, fungi, protozoa, and helminthes) (Chen & Carlson, 2008). Organisms that have been implicated include *Neisseria meningitides*, *Neisseria gonnorhoeae*, *Pseudomonas*, *Staphylococcus aureus*, *Hemophilus influenzae*, *Streptococcus*, *and Rickettsia* (Carlson & Chen, 2006).

Cutaneous findings include hemorrhagic petechiae, pustular purpura, vesicles, bullae, erythematous macules, and nodules surrounded by pustules (Carlson & Chen, 2006). Patients with chronic gonococcemia and chronic meningococcemia typically present with petechiae surrounded by a rim of erythematous vesicles and pustules with a necrotic surface on the extremities, particularly acral surfaces (Chen & Carlson, 2008).

Biopsy reveals a mixed small and medium sized vessel neutrophilic vasculitis of deep dermal and subcutaneous vessels (see Figure 14) (Chen & Carlson, 2008). Vessel occlusion with thrombi composed of platelets and red blood cells is also seen (Sotto et al., 1976). As compared to conventional small vessel neutrophilic vasculitis, septic vasculitis has scant perivascular fibrin and fibrin thrombi and little to no nuclear debris (Carlson, 2010). Arteriolar involvement, hemorrhage, and subepidermal and intraepidermal pustules help distinguish septic vasculitis from cutaneous leukocytoclastic angiitis (Shapiro et al., 1973). Epidermal changes include edema, intra-epidermal or subcorneal pustules, and epidermal necrosis (Shapiro et al., 1973). Gram stain is typically negative in septic vasculitis, however, gram negative rods can be seen within the cytoplasm of neutrophils, within endothelial cells, and admixed with extravasated red blood cells in acute meningococcemia (Sotto et al., 1976). Gram negative diplococci can be isolated in gonococcemia if there is a high bacterial load and if lesions are biopsied early (Ackerman et al., 1965). Deposition of IgG, IgM, IgA, complement, and fibrinogen can be seen on direct immunofluorescence in acute meningococcemia (Sotto et al., 1976).

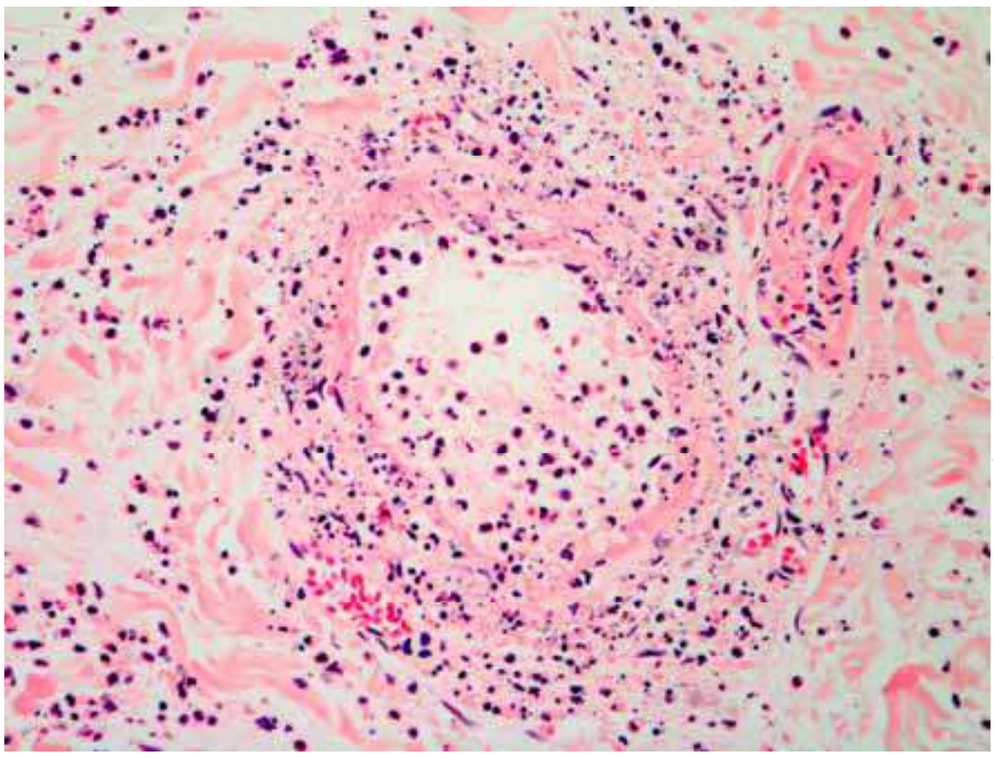


Fig. 14. Septic Vasculitis. Note the distinct neutrophilia and abundant karyorrhectic debris and near complete destruction of the vessel wall (H&E, 200x).

2.2.5 Behçet's disease

Behçet's disease (BD) is a chronic inflammatory disease characterized by oral and genital ulcers, arthralgias, gastrointestinal symptoms, and central nervous system involvement (Chen et al., 1997). Cutaneous manifestations include erythema nodosum like nodules, follicular lesions, or papulopustular lesions or rarely can include palpable purpura, hemorrhagic bullae, erythema multiforme like lesions, or pyoderma gangrenosum like lesions (Chen et al., 1997).

While BD is typically classified as a neutrophilic dermatosis, recent evidence has suggested that it should rather be categorized as a cutaneous vasculitis (Chen et al., 1997). BD is unique in that it involves the entire spectrum of blood vessels, ranging from capillaries to the aorta (Carlson & Chen, 2006). Biopsy reveals a neutrophilic, and rarely a lymphocytic, vasculitis of medium sized vessels in the subcutis and venules throughout the dermis and subcutis (Chen et al., 1997). Biopsy of erythema nodosum like lesions show a subcutaneous thrombophlebitis with a lymphocytic vasculitis in the overlying dermis (Carlson & Chen, 2006). Fibrinoid necrosis, nuclear dust, panniculitis, venulitis in the dermis and subcutis, and necrotizing venulitis can also be seen (Chen et al., 1997). Direct immunofluorescence rarely shows deposition of IgA, IgM, and/or complement (C3 or C1q) (Chen et al., 1997).

3. Medium sized vessel vasculitis

3.1 Polyarteritis nodosa

Polyarteritis nodosa (PAN) is a relatively rare vasculitis of medium sized vessels which presents equally in men and women between the ages of 40 to 60 years (Carlson & Chen, 2007). While the etiology in most cases of PAN is unknown, there is a strong association with hepatitis B virus (Frankel et al., 2002). Patients may present with a wide range of constitutional symptoms including fever, weight loss, arthralgias, muscle wasting, abdominal pain (usually as a result of bowel infarction and perforation), mononeuritis multiplex, hypertension, orchitis, and congestive heart failure (Colmegna & Maldonado-Cocco, 2005). Renal manifestations in PAN typically include a primary vascular nephropathy presenting as multiple aneurysms in branches of the renal artery which leads to hypertension and rare pulmonary involvement, in contrast to Wegener's granulomatosis and microscopic polyangiitis which presents with glomerulonephritis and frequent pulmonary manifestations (Frankel et al., 2002; Colmegna & Maldonado-Cocco, 2005).

Cutaneous manifestations occur in 20-50% of patients with classic PAN and include palpable purpura, while this is a manifestation of small vessel vasculitis, it does not exclude the diagnosis of PAN (Fiorentino, 2003). Other cutaneous findings indicative of medium sized vessel vasculitis include livedo reticularis, ulcers, and subcutaneous nodules (Fiorentino, 2003). Rare findings include ecchymosis, gangrene, and urticaria (Colmegna & Maldonado-Cocco, 2005).

The classic histologic description of PAN requires the presence of a necrotizing vasculitis in medium sized vessels (see Figure 15) (Colmegna & Maldonado-Cocco, 2005). Four stages of histologic findings in PAN have been identified: degenerative, acute inflammatory, granulation tissue, and healed end-stage (Arkin, 1930). The degenerative

stage shows destructive coagulative necrosis of the media, fibrinous exudates surroundings the internal elastic lamina, neutrophilic infiltration, and partial destruction of the internal and external elastic lamina (Arkin, 1930). The acute inflammatory stage is characterized by infiltration of neutrophils, lymphocytes, and eosinophils, complete destruction of the internal elastic lamina, fibrinous exudates extending from the intima to the adventitia with complete destruction of the media, fibroblastic proliferation and edematous changes of the surrounding connective tissue, and total obliteration of the vessel lumen with fibrin thrombi (Arkin, 1930). In the granulation tissue stage, neutrophils are replaced by increasing numbers of lymphocytes, marked granulation tissue that replaces the media and extends into the adventitia and can invade through defects in the internal elastic lamina into the vessel lumen, and prolific intimal thickening (Arkin, 1930). The final stage, healed granulation tissue stage, is characterized by acellular scar tissue replacing the arterial wall and perivascular fibroblastic proliferation (Arkin, 1930).

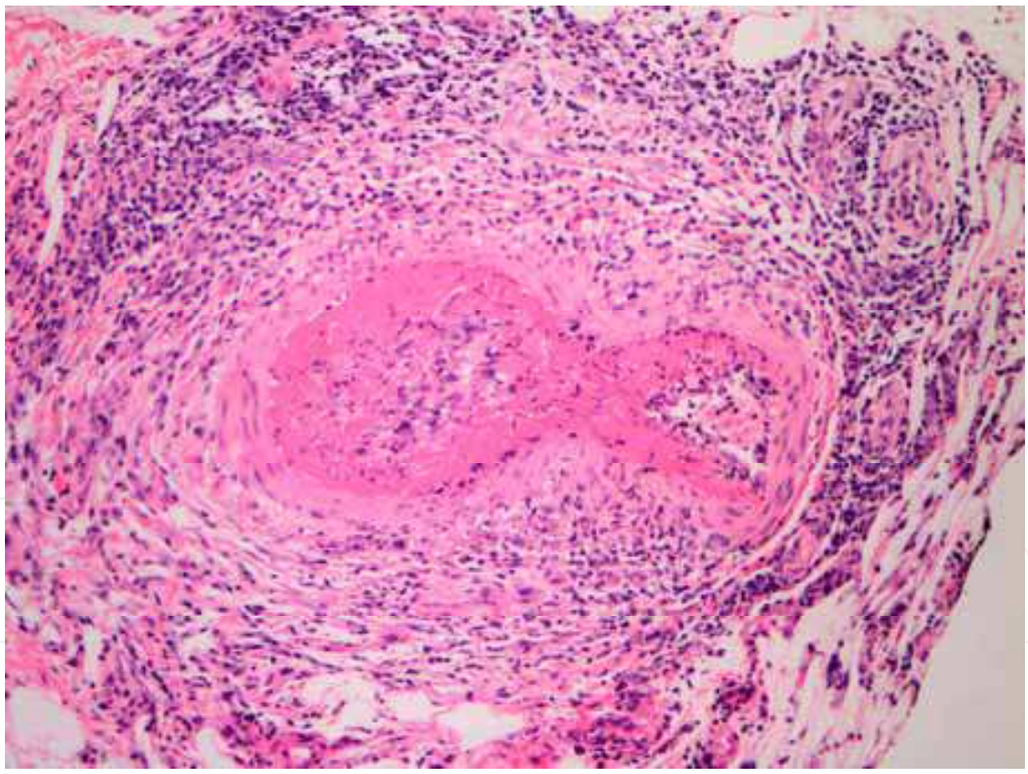


Fig. 15. Polyarteritis Nodosa. Necrotizing vasculitis in a medium sized vessel (H&E, 100x).

When an ulcerated lesion is present, a biopsy including adequate subcutis central to the ulcer border is essential to optimize the diagnostic yield (Ricotti et al., 2007). Biopsy of ulcerated lesions will demonstrate a vasculitis of medium sized vessels at the dermal subcutaneous junction with associated neutrophilic infiltration, leukocytoclasia, and endothelial swelling with overlying dermal fibrosis and necrosis and epidermal ulceration

(Ricotti et al., 2007). Lesions which present as subcutaneous nodules show a neutrophilic vasculitis of medium sized muscular vessels with a predilection for areas where arteries bifurcate (Carlson & Chen, 2007).

3.1.1 Cutaneous polyarteritis nodosa

Cutaneous polyarteritis nodosa (CPAN) is a limited form of PAN which presents with cutaneous findings, fever, myalgias, arthralgias, and peripheral neuropathy, but no other systemic symptoms (Fiorentino, 2003). It typically affects women more then men between the ages of 20 to 40 years (Chen & Carlson, 2008). Classic cutaneous manifestations include tender subcutaneous nodules which are usually limited to the lower extremities and buttocks (Carlson & Chen, 2007). Ulcerations with surrounding irregular livedo reticularis in a "burst" pattern are common in CPAN (Morgan & Schwartz, 2010). Other cutaneous findings include petechiae, purpura, necrosis, and gangrene (Morgan & Schwartz, 2010). Ulcerated lesions are more frequently found in patients with associated neuropathy and rare reports exist of these patients eventually progressing to classic PAN (Chen & Carlson, 2008). Patients with mononeuritis multiplex may also present with atrophie blanche without evidence of venous insufficiency and/or thrombophilia (Carlson & Chen, 2007). While patients with classic PAN can present with similar cutaneous findings, the lack of systemic multi-organ involvement in CPAN is an essential distinction between the two diseases (Morgan & Schwartz, 2010).

The clinical severity of CPAN can be graded into three classes: class I or mild disease presents with subcutaneous nodules, livedo reticularis, and/or mild polyneuropathy; class II or severe disease presents with livedo, painful ulcerations, sensory neuropathy, fever, malaise, and arthralgia; and class III or progressive systemic disease presents with fever, malaise, arthralgia, deep ulcerations, necrotizing livedo, acral gangrene, foot drop mononeuropathy multiplex, worsening musculoskeletal symptoms, positive autoimmune serology, and eventual systemic involvement (Chen & Carlson, 2008).

Similar to classic PAN, the etiology of CPAN is usually unknown although there is an association between CPAN and Group A β hemolytic Streptococcus, hepatitis B (although this association is not as well documented in CPAN as it is in classic PAN), hepatitis C, parvovirus B-19, tuberculosis, and minocycline (Morgan & Schwartz, 2010).

The traditional description of CPAN on deep skin biopsy is a neutrophilic, necrotizing vasculitis of small to medium sized muscular arteries at the dermal-subcutaneous junction (Morgan & Schwartz, 2010). Similar to classic PAN, four stages of histologic findings in CPAN have been described;, however, the progression of arterial destruction is different in CPAN than classic PAN. The acute stage is characterized by a neutrophilic vasculitis of small to medium sized blood vessels and the dermal subcutaneous junction, damage to endothelial cells, fibrin thrombi within the vascular lumen, and no disruption of the internal elastic lamina (Ishibashi & Chen, 2008). The subacute stage shows focal disruption of the internal elastic lamina with fibrinoid necrosis of the media adjacent to the disruption, a targetoid appearance of vessels caused by subendothelial fibrinoid necrosis lined by an inner layer of intact endothelial cells and surrounded by the internal elastic lamina, and infiltration of the vessel wall by neutrophils, lymphocytes, and histiocytes (Ishibashi & Chen, 2008). The reparative stage shows a shift in the inflammatory cells to mostly lymphocytes and histiocytes, complete occlusion of the vascular lumen by fibrin thrombi,

and fibroblastic proliferation (Morgan & Schwartz, 2010). The healed stage shows discernible thickening of the intima with a scant inflammatory infiltrate surrounding the artery and perivascular neovascularization (Ishibashi & Chen, 2008). Direct immunofluorescence frequently reveals IgM and C3 deposition in and around deep dermal vessels, however, interestingly, IgG and IgA are almost universally negative in all cases of CPAN (Diaz-Perez et al., 1980). Since the histologic features diagnostic of CPAN, including neutrophilic vasculitis of medium sized vessels and the dermal subcutaneous junction, are segmental and focal, repeated and deeper biopsies followed by serial sectioning may be required for diagnosis (Chen & Carlson, 2008).

The main diagnostic challenge for clinicians and dermatopathologists is the distinction between CPAN and thrombophlebitis. Thrombophlebitis is a vasculitis involving veins and venules while CPAN affects arteries (Chen, 2010). The distinction between veins and arteries is an important one in differentiating these two conditions. Features that histologically define an artery include a round vessel with a concentric, continuous wreath of smooth muscle fibers and a band of wavy elastic fibers between the intimal and medial layers of the vessel wall known as the internal elastic lamina while features of a vein include oval vessels with collagen admixed with smooth muscle and elastic fibers, but lacks an internal elastic lamina (Carlson, 2010). The presence or absence of an internal elastic lamina has long been cited by pathology textbooks as the distinction between arteries and veins, however, this distinction is blurred by increased hydrostatic pressure in the lower extremities which causes hypertrophy of the muscular layer and proliferation of elastic fibers in veins which can resemble the muscular layer and internal elastic lamina of arteries (Dalton et al., 2006). In fact, up to 44% of veins demonstrate an internal elastic lamina-like layer (Dalton et al., 2006). Three possible solutions have been suggested to avoid this diagnostic pitfall. The muscular pattern in arteries demonstrates a continuous wreath of smooth muscle while veins show bundles of smooth muscle admixed with collagen (Dalton et al., 2006). Next, the internal elastic lamina of an artery has an even thickness while the internal elastic lamina-like layer seen in veins is thinner and uneven in thickness (Chen, 2010). It is important to note, however, that the internal elastic lamina seen in arteries can lose its regular wavy appearance and thickness during the healing stages of arteritis (Ishiguro & Kawashima, 2010). Perhaps the most helpful tool in the histological distinction of a vein and artery is the use of an elastic stain which will demonstrate numerous elastic fibers in the muscular layers of a vein, but only scant fibers in the muscular layers of an artery (Chen, 2010).

3.2 Kawasaki disease (also known as mucocutaneous lymph node syndrome)

Kawasaki disease typically occurs in children less than four years of age and is defined clinically as a fever of 1-2 weeks duration which is unresponsive to antibiotics in conjunction with a constellation of symptoms including non-exudative conjunctivitis, oral manifestations (dry lips, strawberry tongue, etc.), erythematous and edematous palms and soles, polymorphous rash, and cervical lymphadenopathy (Hirose & Hamashima, 1978; Weston & Huff, 1981). Presence of at least five of the previously mentioned symptoms or four of the symptoms plus evidence of coronary artery aneurysm should be identified to diagnose Kawasaki disease (Kimura et al., 1988). The most feared complication of Kawasaki disease is a coronary artery aneurysm which develops in 20-25% of untreated patients and is the leading cause of acquired heart disease in children (Gedalia & Cuchacovich, 2009).

Cutaneous changes include edema and redness of the palms and soles which evolves into a macular eruption beginning on the extremities and spreading to the trunk (Kawasaki et al., 1974). The eruption then progresses into a morbilliform, scarlatiniform, or multiform eruption (Kawasaki et al., 1974). The morbilliform lesions consist of generalized macular and papular lesions which are clinically indistinguishable from a viral exanthem (Weston & Huff, 1981). The scarlantiniform eruption mimics the rash seen in scarlet fever or a drug eruption (Weston & Huff, 1981). The multiform lesions are typically targetoid lesions which do not progress to form blisters and can resemble erythema multiforme (Weston & Huff, 1981). Rarely patients can present with pustules superimposed on erythema (Kimura et al., 1988). Regardless of the initial presentation of the eruption, all patients advance to desquamation beginning in the periungual regions and progressing centrally to the trunk, a finding characteristic of but not unique to Kawasaki disease (Kawasaki et al., 1974).

Skin biopsies reveal a superficial perivascular dermatitis characterized by dermal edema and mild perivascular lymphocytic inflammation (Weston & Huff, 1981). Papillary edema and minimal extravasation of red blood cells can be seen if the exanthem is biopsied within six days of onset (Hirose & Hamashima, 1978). Deposition of fibrinoid material and focal endothelial cell necrosis has been reported (Hirose & Hamashima, 1978). Vessel changes are most prominent in the medium sized vessel of the subcutis (Carlson & Chen, 2007). The pustular lesions show intraepidermal neutrophilic pustules, epidermal hyperplasia, superficial perivascular infiltrate with lymphocytes, neutrophils, and histiocytes, and neutrophilic inflammation around intraepidermal eccrine ducts (Kimura et al., 1988). Other diseases which present histologically with intraepidermal pustules such as pustular psoriasis, subcorneal pustular dermatosis, staphylococcal scalded skin syndrome, and milia should also be considered in the differential diagnosis (Kimura et al., 1988). Rare cases of psoriasiform-like hyperkeratosis have been reported (Passeron et al., 2002).

3.3 Nodular vasculitis (also known as erythema induratum or erythema induratum of bazin)

Nodular vasculitis (NV) is characterized by tender, indurated plaques on the calves of young to middle aged women and is associated with *Mycobacterium tuberculosis* (Schneider JW, 1997). The prodromal phase of NV occurs 1-3 weeks prior to the onset of lesions and consists of fever, malaise, arthritis, and arthralgias (Gilchrist & Patterson, 2010). NV presents as reoccurring crops of lesions lasting 2 weeks which heal with residual scarring and hyperpigmentation (Segura et al., 2008).

Histologically, lobular panniculitis with necrotizing vasculitis that can be neutrophilic, lymphocytic, or granulomatous, is seen (see Figure 16) (Carlson & Chen, 2007). Early lesions show neutrophilic infiltration between fat lobules while established lesions show granulomatous infiltration of lobules (Segura et al., 2008). Two types of lesions can be seen. Type I is characterized by focal panniculitis and neutrophilic vasculitis of muscular vessels (Schneider & Jordaan, 1997). Type II lesions are characterized by diffuse septolobular panniculitis with numerous foci of neutrophilic small and medium sized vessel vasculitis (Schneider & Jordaan, 1997). Neutrophilic septal venulitis and arteritis is also common (Segura et al., 2008). Caseous necrosis can also be seen extending to the epidermal surface (Segura et al., 2008).

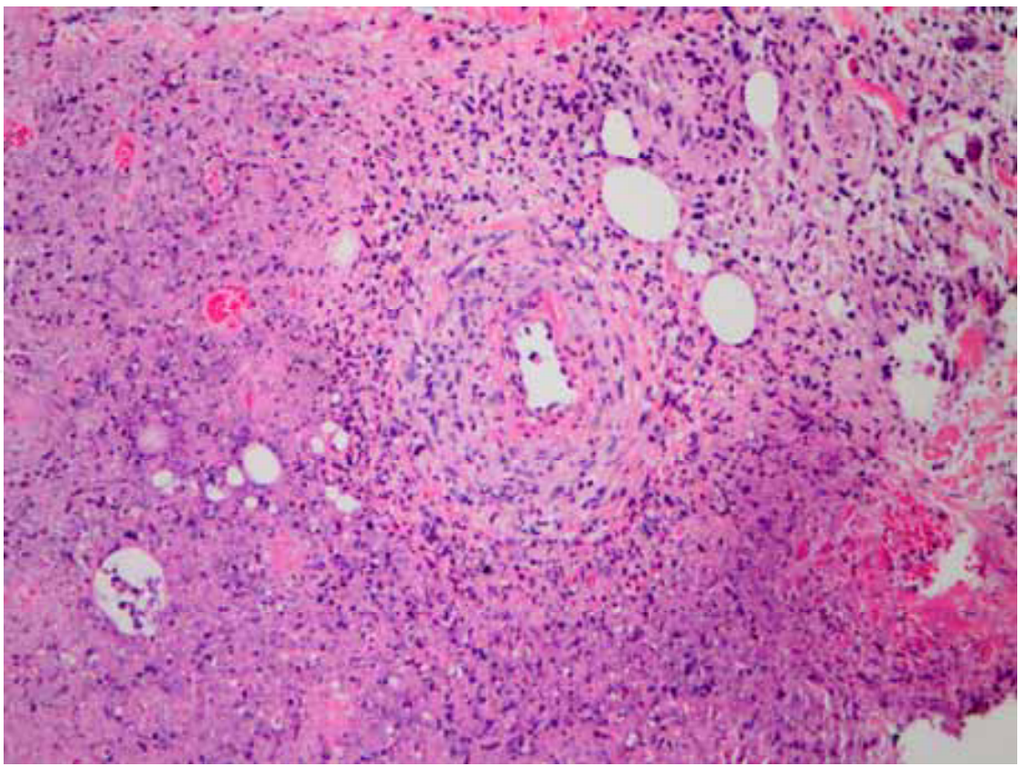


Fig. 16. Nodular Vasculitis. Suppurative necrosis of the subcutaneous fat surrounds this deep, inflamed vessel (H&E, 100x).

4. Large vessel vasculitis

4.1 Takayasu arteritis

Takayasu arteritis (TA) is a large vessel granulomatous arteritis which typically involves the aorta and its main branches (Carlson & Chen, 2007). Patients are more commonly female in their second to third decade of life (Gedalia & Cuchacovich, 2009). The initial symptoms are nonspecific and usually consist of fever, fatigue, myalgias, arthralgias, and weight loss (Frankel et al., 2002). The most common clinical presentation is arterial hypertension, however, patients can also present with cardiac failure, bruits, and pulselessness (Gedalia & Cuchacovich, 2009). Other symptoms resulting from vessel occlusion and ischemia include claudication, syncope, headache, and visual disturbances (Frankel et al., 2002). Stenosis or aneurysm of the aorta or its major branches seen on angiography is the gold standard for the diagnosis of TA (Gedalia & Cuchacovich, 2009).

Cutaneous involvement is rare in TA, occurring in 8-28% of patients (Carlson & Chen, 2007). Clinical findings include erythematous nodules, pyoderma gangrenosum-like ulcer, erythema nodosum, erythema induratum, and purpura (Perniciaro et al., 1987).

During the acute phase of TA, the characteristic findings of granulomatous arteritis with transmural inflammation can be seen in the aorta or its branches (Lie, 1990). The morphologic findings on skin biopsy are generally non-specific and include granulomatous vasculitis, necrotizing vasculitis of the deep dermal medium sized vessels, and septal and lobular panniculitis with or without vasculitis (Pascual-Lòpez et al., 2004).

4.2 Giant cell arteritis (also known as temporal arteritis)

Giant cell arteritis (GCA) is a granulomatous vasculitis of large arteries, particularly affecting the branches of the external carotid artery (Tsianakas et al., 2009). The prevalence is higher in women, the elderly, Caucasians, and patients with polymyalgia rheumatica (Chen & Carlson, 2008). Clinical symptoms are usually due to ischemia secondary to endarteritis obliterans and include headache, jaw cladication, and visual and neurological problems (Carlson & Chen, 2007). Timely diagnosis is imperative since significant morbidity, including visual loss, and even death may occur if treatment is delayed (Goldberg et al., 1987).

Cutaneous findings in GCA are rare, presenting in less than 1% of cases, and include scalp tenderness, loss or decrease in temporal pulse, scalp necrosis, and scalp blanching (Chen & Carlson, 2008). Erythema, ecchymoses, purpura, ulceration, gangrene, urticaria, erythema nodosum, and hyperpigmentation on the lower extremities have also been reported (Goldberg et al., 1987). Scalp necrosis is associated with increased risk of vision loss and carries a higher mortality rate (Tsianakas et al., 2009).

The diagnostic features of GCA on temporal artery biopsy are segmental inflammation of the artery and infiltration of the media, adventitia, and internal elastic lamina by lymphocytes, neutrophils, and multinucleated giant cells (see Figures 17 and 18) (Goldberg et al., 1987). The segmental arterial involvement makes histologic diagnosis a challenge.

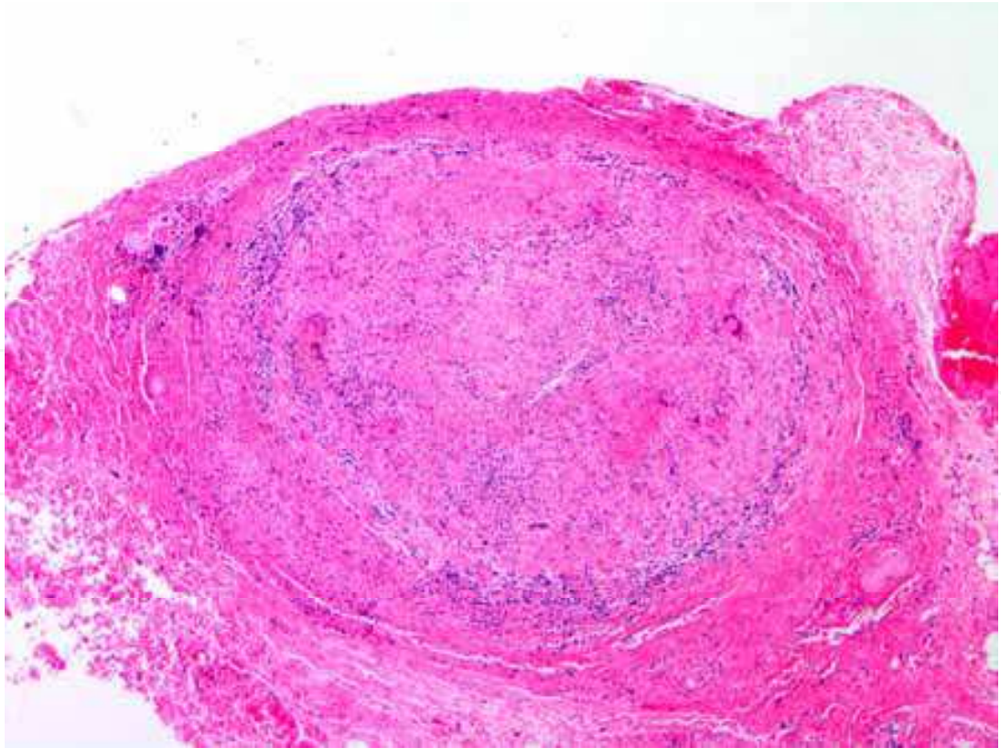


Fig. 17. Giant Cell (Temporal) Arteritis. A dense granulomatous infiltrate effaces the elastic artery. The intima and media are particularly affected and giant cells may be conspicuous (H&E, 40x).

Lack of histologic evidence of GCA on temporal artery biopsy should not delay treatment in a patient clinically suspected of having GCA (Lie, 1990). Elastophagocytosis is a common finding (Carlson & Chen, 2007). Granulomatous infiltration of medium sized muscular vessels in the deep dermis or subcutaneous tissue is typically seen on skin biopsy (Chen & Carlson, 2008). Healing lesions are characterized by segmental stenosis and loss of the elastic lamina as well as myxomatous stromal replacement of the vessel wall (Carlson & Chen, 2007). The lack of inflammation seen in completely healed lesions makes the distinction between GCA and atherosclerosis impossible (Carlson & Chen, 2007).

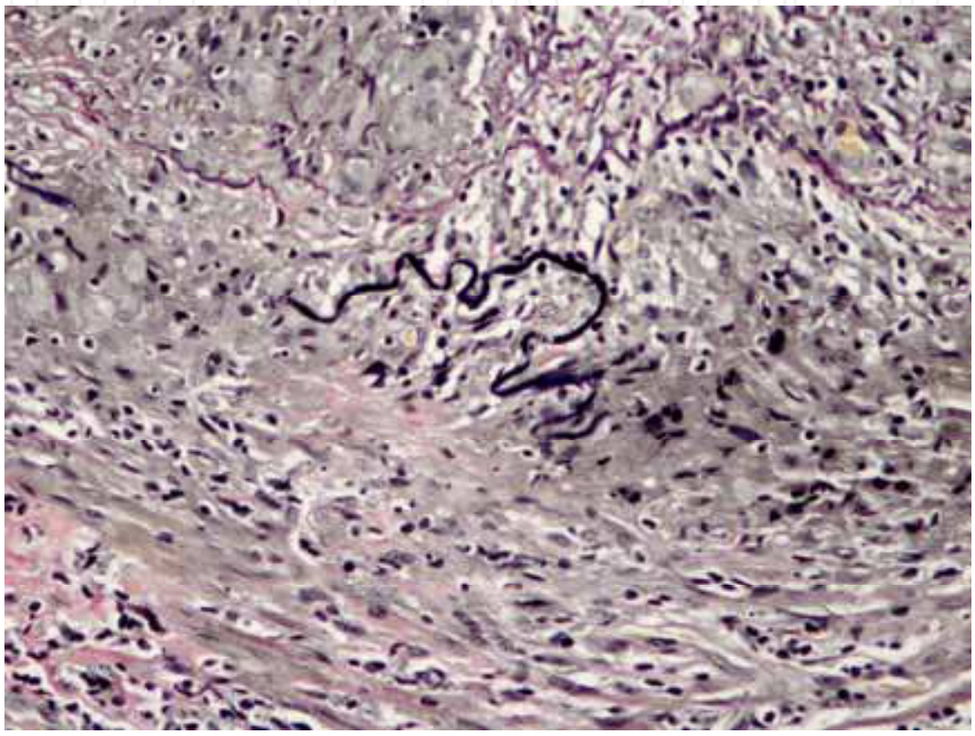


Fig. 18. Giant cell arteritis. Staining for elastin fibers demonstrates fragmentation of the internal elastic lamina (elastic von Giesen stain, 200x).

5. Conclusion

Vasculitis is a broad, poorly defined category of diseases. The clinical presentation, progression of disease, and treatment vary as widely as the diseases themselves. Often times it is the compilation of clinical, laboratory, and pathologic findings which aid in formulating the diagnosis.

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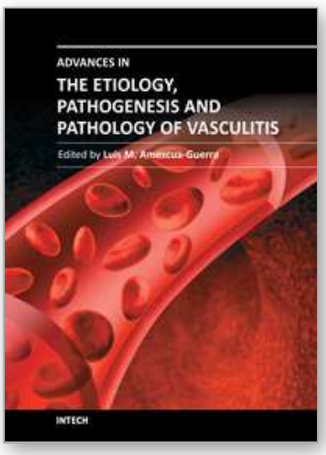
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This book represents the culmination of the efforts of a group of outstanding experts in vasculitis from all over the world, who have endeavored to devote their work to this book by keeping both the text and the accompanying figures and tables lucid and memorable. Here, you will find an amalgam between evidence-based medicine to one based on eminence, through an exciting combination of original contributions, structured reviews, overviews, state-of the-art articles, and even the proposal of novel pathogenetic models of disease. The book contains contributions on the etiology and pathology of vasculitis, the potential role of endothelial cells and cytokines in vascular damage and repair as well as summaries of the latest information on several primary and secondary vasculitis syndromes. It also covers selected topics such as organ-specific vasculitic involvement and quality of life issues in vasculitis. The editor and each of the authors invite you to share this journey through one of the most exciting fields of the medicine, the world of Vasculitis.

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