

## Vasculitis in Children

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Vasculitis implies a straightforward process, inflammation of blood vessels. The conditions included in this category are anything but straightforward, however, because of the variability of vessels that may be involved and the multitude of ways in which they may be affected. Thus, damage to mural structures can lead to anything from numbness to pain, thrombosis to bleeding, aneurysm formation to necrosis.

Further confounding the study of vasculitides in children are the large gaps in the understanding of the nosology, etiology, and pathogenesis of these entities. This lack of understanding, in turn, complicates attempts at classification, hampers clinicians' ability to quantify prognosis, and thwarts rationalization of therapy. This article begins with a general overview of vasculitis, situations in which the diagnosis should be considered, diagnostic methods, and therapeutic considerations. Details and treatments unique to specific vasculitides are then reviewed.

### Diagnosis

Early in the course of a vasculitis, findings are generally nonspecific, primarily reflecting systemic inflammation (fever, malaise, fatigue, failure to thrive, elevated acute-phase reactants). As vessel damage progresses, more characteristic abnormalities, including evidence of vascular compromise on physical examina-

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tion, elevation of markers of vascular injury (eg, von Willebrand's factor antigen, pentraxin 3), and distinctive autoantibodies (especially antineutrophil cytoplasmic antibodies [ANCA] or anti-endothelial antibodies) may be detected. Although these findings are often specific for vasculitis, they are seldom part of a routine screening evaluation, so a physician often must consider the diagnosis of vasculitis before its manifestations are pathognomonic. Should the diagnosis be delayed beyond this stage, irreversible tissue damage may occur; it is important that therapy be initiated while the findings remain subtle. Thus a "Catch-22" exists: little information specifically suggestive of vasculitis may be apparent when the diagnosis needs to be made; the condition tends to become more evident only after severe and irreversible morbidity is present.

Despite the inherent variability of the manifestations of vasculitis, certain specific symptoms are particularly suggestive of vascular inflammation. Involvement of large- or medium-sized muscular arteries, as may be seen in Takayasu arteritis (TA) or polyarteritis nodosa (PAN), initially causes symptoms related to the severity of the inflammatory response. As vascular compromise progresses, symptoms of arterial insufficiency begin to dominate. Involvement of large vessels to the extremities, such as the subclavian or femoral arteries, typically leads to claudication, whereas involvement of visceral vessels causes hypertension (renal arteries), abdominal pain (mesenteric and celiac axes), chest pain (aortic or coronary artery involvement), or neurologic symptoms (focal neurologic deficits or neuropathic pain).

Inflammation of smaller arteries and arterioles leads to symptoms in richly vascularized organs. Skin involvement—livedo reticularis, purpuric (generally palpable) or nonblanching lesions, and palmar or plantar rashes—is most suggestive of vascular inflammation. Pulmonary, renal, and gastrointestinal arterial beds are often involved as well. Consequently, hemoptysis, hematuria, hypertension, abdominal pain, or melena may signify the development of vessel damage. Capillary and venous inflammation typically involves the same organs, although the lower volume of blood flow through these vessels tends to make capillaritis and venulitis less of an acute emergency than arteritis.

Whenever vasculitis is considered as a diagnosis, a thorough history and careful general physical examination should be augmented by focus on clinical features of vascular disease. History should include recent illnesses, in particular infections, other exposures (including prescription and over-the-counter drugs), travel, and family history. All pulses must be palpated carefully, and bilateral Allen's tests should be performed to confirm patency of the radial and ulnar arteries and volar arch. The neck, abdomen, and proximal extremities should be auscultated for bruits, and blood pressures in all four extremities should be compared for asymmetry. The skin should be examined carefully for lesions that are nodular or do not blanch, and the two other windows on small vessel abnormalities—ocular fundi and nailbed capillaries—should be assessed as well.

Laboratory studies specific for the diagnosis of vasculitis are not yet available. When vasculitis is being considered, laboratory investigation should include a complete blood cell count and acute-phase reactants (especially erythrocyte

sedimentation rate [ESR] and C-reactive protein [CRP]) for evidence of systemic inflammation. Ongoing immune activation leads to hypergammaglobulinemia in many cases of systemic vasculitis. Certain small-vessel diseases are characterized by ANCA. Von Willebrand factor antigen is released by damaged vascular endothelium, so it is elevated in small-vessel vasculitides but also in other conditions that cause vessel damage, including stroke, trauma, and severe infections [1]. New assays currently under development, including measurement of PTX3, a pentraxin expressed by endothelial cells and monocytes [2], hold promise as more sensitive and specific markers of diffuse vascular inflammation, but they are not yet routinely available.

Imaging procedures should be used to confirm a clinical suspicion of vasculitis, not to hunt blindly for a diagnosis. When pulmonary involvement is suspected, pulmonary function tests and imaging of the lungs with radiographs or CT are often useful. Vascular imaging must be interpreted in light of clinical and laboratory data unique to the individual case. Doppler ultrasound studies and CT or MRI angiograms are adequate for resolving abnormalities in large- or medium-sized vessels, but conditions involving smaller vessels often can be visualized only by use of focused angiograms. Even in the hands of interventional radiologists experienced in pediatric angiography, these procedures are potentially morbid, so careful attention to history and physical examination should be relied upon to minimize the number of unnecessary studies.

The reference standard for diagnosing a vasculitis remains histopathologic demonstration of vascular inflammation, although tissue specimens may not be available in many cases because of the inaccessibility of lesions or patchiness of the vascular involvement. When skin lesions are present, deciding to obtain a biopsy is relatively easy; when inaccessible structures such as the brain are involved, calculating the risks and benefits of a biopsy is significantly more complicated.

## Classification

Primary vasculitides may be classified according to their clinical manifestations, the size of blood vessels involved, the histology of vascular damage, or the presumed disease pathogenesis. An etiologic classification system would be ideal, especially because it could potentially shed light on anticipated responsiveness to treatment. For example, in adults, inhibition of tumor necrosis factor (TNF) seems to be effective in TA [3] but apparently is less so in Wegener's granulomatosis [4]. On the other hand, using rituximab to target B cells seems to be uniquely safe and effective in ANCA-associated vasculitides [5]. This information might warrant empiric use of rituximab in other vasculitides associated with autoantibodies (eg, anti-endothelial antibodies) but perhaps not in cases of vascular damage caused by cell-mediated mechanisms.

Most current classification systems are based on a combination of histologic and clinical features of the vasculitides [6]. Unfortunately, as new data emerge, conditions previously thought to be similar turn out to differ in fundamental

**Box 1. Classification of pediatric vasculitides***Primary vasculitides**Large vessel diseases*

- Takayasu arteritis
- Giant cell (temporal) arteritis

*Medium vessel disease*

- Polyarteritis nodosa
  - Cutaneous
  - Systemic
  - Cogan's syndrome
- Kawasaki disease

*Small-vessel disease*

- Henoch-Schönlein purpura
- Hypersensitivity vasculitis
- Primary angiitis of the central nervous system

*ANCA-positive vasculitis*

- Wegener's granulomatosis
- Microscopic periarteritis
- Churg–Strauss syndrome

*Secondary vasculitides**Infection-related vasculitis*

- Hepatitis viruses
- Herpes viruses (EBV, CMV, varicella)

*Vasculitis secondary to connective tissue disease*

- Dermatomyositis,
- Systemic lupus erythematosus,
- Rheumatoid arthritis
- Hypocomplementemic uticular vasculitis

*Drug hypersensitivity –related vasculitis**Malignancy-related vasculitis**Post–organ transplant vasculitis**Pseudovasculitic syndromes*

- Myxoma
- Endocarditis
- Sneddon syndrome

*Vasculitides with strong genetic component*

- Periodic fever syndromes
- Behçet's disease

*Modified from* Hunder GG, Wilking AP. Classification of the vasculitides in children. UpToDate, 2005. Available at: <http://www.uptodate.com/application/search.asp>. Accessed February 14, 2005.

ways. Thus, PAN, first described pathologically by Rokitansky in 1852 [7], classically refers to a medium-sized muscular arteritis. Although most cases involve both visceral and cutaneous vessels, some show a particular predilection for the skin (cutaneous PAN), or involve the eyes and ears (Cogan's syndrome). Most recently, with the discovery that some patients with PAN demonstrate antibodies to myeloperoxidase, ANCA-positive microscopic PAN was added to the nomenclature. The result is that today the name PAN might refer to a bewildering array of conditions, some of which are limited, others systemic, some benign, others life-threatening. Clearly, such a classification system requires modification, but the tools for doing so in a coherent manner remain elusive [8].

No classification system is infallible, and a certain degree of overlap is unavoidable. Recently, for example, a young patient of the authors was diagnosed as having primary angiitis of the central nervous system (CNS) on the basis of a brain biopsy. Three years later, he was found to have Hodgkin's lymphoma, a condition associated with vasculitis of the CNS in adults. Should his condition retrospectively be reclassified as a vasculitis secondary to a malignancy? Because this form of vasculitis generally remits when the underlying tumor is treated, this reclassification would be reasonable from a therapeutic perspective. Nonetheless, both tumor-associated vasculitis and primary angiitis of the CNS accurately describe his condition, according to the knowledge available at the time of classification. Allowing for such ambiguities, the authors include a working scheme for classifying pediatric vasculitides, attempting to include current knowledge of disease pathogenesis but leaving open the possibility of reclassification as new data emerge (Box 1) [104].

## Epidemiology

Vasculitis is rare in children of all backgrounds, although the incidence of particular diseases varies by location, ethnicity, gender, and underlying conditions. The most complete survey was performed by Gardner-Medwin et al [9] in West Midlands, UK, in 2002. The overall estimated annual incidence of primary vasculitis among children under 17 years of age was 20.4/100 000, with Henoch-Schönlein purpura (HSP) the most prevalent. The Pediatric Rheumatology Database Group reported that 3.3% of children followed at 26 pediatric rheumatology referral centers in the United States carried a diagnosis of vasculitis between 1992 and 1995 [10]. This percentage probably represents an underestimate, because children with HSP or Kawasaki disease (KD) are often treated by pediatricians and not referred to specialty care centers.

## Pathogenesis

Despite extensive research, mechanisms underlying the onset and perpetuation of vascular inflammation are generally not understood. Epidemiology, animal

models, basic experiments, and responses to directed therapy are shedding light on the processes involved in a variety of vasculitides, and these studies are mentioned in discussions of specific conditions. More generally, theories of pathogenesis may be divided into the following categories:

1. Humoral factors: Vascular damage secondary to specific antibodies is best demonstrated in the ANCA-associated vasculitides [11]. These antibodies may activate neutrophils, causing vascular inflammation, although the lack of a direct correlation between antibody titers and disease activity suggests that additional factors are important in mediating the vessel damage. Anti-endothelial antibodies are also present in a variety of vasculitides, but whether they are markers or mediators of vascular pathology remains unclear [12].
2. Immune complexes: The size, charge, and immunoreactivity of immune complexes help explain aspects of the pathogenesis of HSP and cryoglobulinemic vasculitis [13]. Similarly, PAN associated with hepatitis B or C seems to be triggered by inflammation incited by immune complexes deposited upon vessel walls [14].
3. T lymphocytes attracted to damaged or infected endothelium may contribute to vascular inflammation through direct cytotoxicity or release of inflammatory cytokines. Evidence of restricted expression of T-cell receptors supports a role for selection of antigen-specific lymphocytes in some types of vasculitis [15]. In addition, suppression of autoreactive lymphocytes may be dependent upon populations of T-regulatory cells. When these cells fail to restrict lymphocyte reactivity with autoantigens, the result may be breaking of tolerance and development of autoimmunity. Once the cycle of immune targeting against blood vessels begins, damage may continue through activation of the complement cascade and recruitment of effector cells such as natural killer cells or phagocytes [16]. Indeed, biopsy samples from different types of vasculitis demonstrate different populations of cells invading vessel walls (eg, macrophages in KD and eosinophils in Churg–Strauss syndrome [CSS]) [17].
4. The characteristic predilection of different vasculitides for different anatomic sites remains unexplained, although it seems to depend on a variety of factors, including specificity of the triggering antigen, regional variations in cell surface receptors, and unidentified contributions of surrounding tissues.

### **Henoch-Schönlein purpura**

The most common pediatric vasculitis is HSP, IgA immune complex-mediated small-vessel leukocytoclastic vasculitis that classically presents with the triad of nonthrombocytopenic palpable purpura, colicky abdominal pain, and arthritis. The major cause of morbidity is renal involvement: although HSP is

mild in most children, it may progress to chronic renal failure in up to 1% of cases. HSP is significantly more prevalent in young children, but cases in older children and adults seem to have a higher propensity for causing significant renal damage [18]. Symptomatic involvement of other organs is not common, although one study found that a large percentage of children with HSP had abnormalities of pulmonary diffusion capacity despite having no respiratory symptoms [19]. In rare cases, CNS or respiratory lesions may lead to hemorrhage with serious sequelae [20].

A wide variety of infections may trigger HSP. Group A streptococcus is the most common precipitant, demonstrable in up to one third of cases, but exposure to *Bartonella*, *Haemophilus parainfluenza*, and numerous vaccines and drugs may precede the development of HSP [21]. Consistent with the contribution of infectious triggers in children, HSP seems to be slightly more common in boys than in girls, and it occurs more commonly during winter and spring than during warmer months. In adults, however, HSP is reported most frequently in the summer, suggesting different predisposing factors in these cases.

Skin involvement in HSP may begin as urticaria, but in most cases it progresses to dramatic purple, nonblanching lesions (Fig. 1). The disease seems to be mediated by activation of the alternate pathway of complement by large IgA-containing immune complexes [22]. This association may explain the predilection of skin lesions for the lower legs and buttocks in ambulatory children and the sacrum, ears, and buttocks in infants, because gravity causes immune complexes to deposit and incite inflammation in dependent areas.

The arthritis of HSP is usually transient, and it does not cause chronic joint changes or permanent sequelae. Gastrointestinal involvement ranges from colicky abdominal pain to profuse bleeding, intussusception (typically ilio-iliac, unlike intussusceptions associated with infections) and perforation [23]. Pancreatitis, cholecystitis, and protein-losing enteropathy may also occur [24]. Frequently, gastrointestinal symptoms follow the rash; when they occur first, distinguishing appendicitis or other abdominal catastrophes from HSP may be quite challenging [25].



Fig. 1. Typical lower extremity palpable purpura seen in HSP.

In most cases, renal disease is observed early in the disease course, during the first days or weeks. One series found that nephritis occurred within the first 3 months of the illness in 97% of patients [26]. In this study, risk factors for renal involvement included age over 47 years, gastrointestinal bleeding, purpura of more than 1 month's duration, factor XIII activity less than 80% of normal, and factor XIII concentrate treatment. HSP recurs in about one third of patients, especially those with nephritis. It usually recurs during the first 4 to 6 months of the disease. Recurrent episodes resemble the initial presentation, although they are generally less severe, and they do not adversely impact prognosis.

In general, long-term outcomes in HSP are quite good. The major exception is patients with significant kidney involvement, although some female patients with milder renal involvement nonetheless seem to develop hypertension and proteinuria during pregnancy [27]. More generally, there is a correlation between the severity of urinary abnormalities and the chances of developing chronic renal disease, with patients demonstrating both nephritic and nephrotic changes at greatest risk. Renal biopsy is useful for confirming the extent and severity of nephritis and planning treatment: the higher the percentage of glomeruli with crescents, the more likely is development of end-stage renal disease [28]. In a research setting, high serum levels of nitric oxide and urinary nitrate excretion [29], and increased urinary excretion of the tubular proteins *N*-acetyl b-D-glucosaminidase and  $\alpha$ -1-microglobulin also proved useful in identifying patients at higher risk of long-term renal disease [30]. Overall, about 1% to 5% of HSP patients develop some degree of chronic renal disease. Another study found that nailfold capillary abnormalities may be detected well after clinical symptoms remit, suggesting that subclinical vasculitis persists longer than may be readily apparent [31].

HSP most commonly must be distinguished from two other purpuric conditions of childhood: acute hemorrhagic edema of infancy and hypersensitivity vasculitis. Acute hemorrhagic edema of infancy characteristically presents with fever, large purpuric lesions, and edema [32] (Fig. 2). It is a self-limited condition, but clinicians must exclude infectious and noninfectious causes of pur-



Fig. 2. Purpuric rash of acute hemorrhagic edema of childhood. The lesions are larger and more macular than those seen in HSP.

pura before reassuring parents that the rash is likely to resolve within weeks. Hypersensitivity vasculitis is an inflammatory condition of small vessels that occurs after exposure to drugs or infections or may be idiopathic [33]. Histologic evaluation shows leukocytoclastic vasculitis, primarily involving postcapillary venules. Immune complexes are usually present, and mononuclear or polymorphonuclear cells may be present as well. Clinical features include fever, urticaria, lymphadenopathy, arthralgias, low serum complement levels, and elevated ESR. Low serum concentrations of C3 and C4 and the absence of IgA deposition in vessel walls help to distinguish this entity from HSP, in which serum complement levels are normal.

Therapy of HSP is primarily supportive, aiming for symptomatic relief of arthritis and abdominal pain. Acetaminophen or nonsteroidal anti-inflammatory drugs (NSAIDs) seem to be effective in most cases; there is no evidence that these agents increase the likelihood of gastrointestinal hemorrhage in HSP. Use of steroids in children who do not respond to NSAIDs or in those thought to be at highest risk of developing renal compromise continues to be controversial. Prednisone, at a dose of 2 mg/kg/day, seems to relieve symptoms rapidly in most cases, but caregivers must avoid excessively rapid tapering of the steroids, because precipitate tapers commonly trigger a flare of symptoms [34]. More potent immunosuppressive agents, such as cyclophosphamide or azathioprine, are reserved for children with biopsy-proven crescentic glomerulonephritis or other life-threatening complications such as cerebral or pulmonary hemorrhage [35].

## **Kawasaki disease**

### *Etiology and epidemiology*

Although KD or mucocutaneous lymph node syndrome is classified as a vasculitis, it is unique in several respects. Unlike other inflammatory conditions of blood vessels, it is a self-limited condition, with fever and manifestations of acute inflammation lasting for an average of 12 days without therapy [36]. It is diagnosed by clinical criteria (Box 2) [105], not histology or angiography. It is almost entirely a disease of children, with 80% to 90% of cases occurring before the fifth birthday. For all of its similarities to infectious exanthema of childhood, however, KD is not necessarily a benign disease: historically, up to 1.5% of untreated children died from KD.

More than 100,000 cases of KD have been registered in Japan since its initial description in 1967 [37]. Genetic factors seem to account for the varying susceptibility of different ethnic groups to KD, with polymorphisms of chemokines and TNF receptors and variations in HLA haplotypes all possibly contributing. Overall, Asians are affected 5 to 10 times as frequently as whites; blacks and Hispanics have an intermediate risk [38].

The cause of KD remains unknown. As in other vasculitides, blood vessel damage seems to result from an aberrant immune response leading to endothe-

**Box 2. Criteria for diagnosis of Kawasaki disease**

Fever lasting 5 days or more (4 days if treatment with IVIG eradicates fever) plus at least four of the following clinical signs not explained by another disease process (numbers in parentheses indicate the approximate percentage of children with KD who display the criterion):

1. Bilateral conjunctival injection (80%–90%)
2. Changes in the oropharyngeal mucous membranes (including one or more of the following symptoms: injected or fissured lips, strawberry tongue, injected pharynx) (80%–90%)
3. Changes in the peripheral extremities, including erythema or edema of the hands and feet (acute phase) or periungual desquamation (convalescent phase) (80%)
4. Polymorphous rash, primarily truncal; nonvesicular (> 90%)
5. Cervical lymphadenopathy: anterior cervical lymph node at least 1.5 cm in diameter (50%)

*Modified from* Centers for Disease Control. Revised diagnostic criteria for Kawasaki disease. MMWR Morb Mortal Wkly Rpt 1990; 39(No. 44-13):27–8.

lial cell injury and vessel wall damage. Pathologically, however, KD seems to be unique: macrophages [17] and IgA-producing plasma cells [39] have been described in the vessel walls, features recognized in no other conditions.

Many aspects of KD suggest that it is caused by a transmissible agent. A synthetic monoclonal IgA antibody was found to bind to an unidentified cytoplasmic component of macrophages within the coronary arteries of 9 of 12 fatal cases of KD but in none of 10 controls [40]. Similar binding to the respiratory epithelium of proximal bronchi was noted in 77% of fatal cases, never in controls. The significance of these findings is unclear, but one interpretation is that a particular respiratory pathogen may be associated with KD.

Many epidemiologic data also support the theory that KD is triggered by a transmissible agent or agents. Boys are affected 50% more commonly than girls, a feature typical of infectious diseases. The average age of children with KD is about 2 years, and occurrence beyond late childhood is extremely rare [41], suggesting a ubiquitous agent to which most people are exposed and become immune by late childhood. Epidemics occurred regularly in the 1980s, and during these outbreaks the average age of patients dropped while the percentage of girls increased, again typical of infections. Nonetheless, suggestions that certain viruses (eg, Epstein–Barr virus, parvovirus, HIV-2) or bacterial toxins (eg, streptococcal erythrogenic toxin, staphylococcal toxic shock toxin) account for the

majority of cases have not been substantiated [42]. Thus, many researchers now believe that KD represents a final common pathway of immune-mediated vascular inflammation following a variety of inciting infections.

### *Clinical manifestations*

Guidelines for the diagnosis of KD were established by Tomisaku Kawasaki in 1967. Diagnosis requires the presence of fever lasting 5 days or more without any other explanation, combined with at least four of five manifestations of mucocutaneous inflammation (Box 2) [34,43]. As with all clinical criteria, these guidelines are imperfect, with less than 100% sensitivity and specificity. Children who do not meet the criteria may have an incomplete or atypical form of KD. In addition, some patients who manifest five or six signs may have other conditions. For example, one study of patients referred for possible KD found that the standard clinical diagnostic criteria for KD were fulfilled in 18 of 39 patients (46%) in whom other diagnoses were established [44].

Kawasaki published his diagnostic guidelines before cardiac involvement was recognized in this disease. Thus, the criteria were never intended to identify children at risk for developing coronary artery abnormalities. Indeed, at least 10% of children who develop coronary artery aneurysms never meet criteria for KD [45]. In an attempt to improve clinicians' ability to diagnose KD in all cases at risk of developing coronary artery changes, an American Heart Association working group has recommended modifications of the criteria [38]. These recommendations have yet to be validated prospectively.

Fever is probably the most consistent manifestation of KD. It reflects elevated levels of proinflammatory cytokines such as TNF and interleukin (IL)-1 that are also thought to mediate the underlying vascular inflammation [46]. The fever is typically hectic, minimally responsive to antipyretic agents, and remains above 38.5°C during most of the illness. Because KD may be so pleomorphic, it should always be considered in a child with prolonged, unexplained fever, irritability, and laboratory signs of inflammation, especially in the presence of other manifestations of mucocutaneous inflammation. Conversely, the diagnosis must be suspect in the absence of fever.

Bilateral nonexudative conjunctivitis is present in as many as 90% of cases of KD. The predominantly bulbar injection typically begins within days of the onset of fever, and the eyes have a brilliant erythema that spares the limbus. Children are also frequently photophobic, and anterior uveitis may develop [47]. Slit-lamp examination may be helpful in ambiguous cases; the presence of uveitis provides further evidence for the diagnosis of KD because it is seen more commonly in KD than in mimics of the vasculitis.

As KD progresses, mucositis often becomes evident. Cracked, red lips and a strawberry tongue are characteristic; the latter is caused by sloughing of filiform papillae and denuding of the inflamed glossal tissue. Discrete oral lesions, such as vesicles or ulcers, as well as tonsillar exudate, suggest a viral or bacterial infection rather than KD.

The cutaneous manifestations of KD are polymorphous. The rash typically begins as perineal erythema and desquamation, followed by macular, morbilliform, or targetoid lesions of the trunk and extremities. Vesicular or bullous lesions are rare.

Changes in the extremities are generally the last manifestation of KD to develop. Children demonstrate an indurated edema of the dorsum of the hands and feet and a diffuse erythema of the palms and soles. The convalescent phase of KD may be characterized by sheetlike desquamation that begins in the periungual region of the hands and feet (Fig. 3) and by linear nail creases (Beau's lines). In addition, one third of children have arthritis. The arthritis is typically a small joint polyarthritis during the first week of illness, followed by a large joint pauci-arthritis. It never persists beyond 1 to 2 months, nor is it erosive.

Cervical lymphadenopathy is the least consistent of the cardinal features of KD, absent in as many as 50% of children with the disease. When present, lymphadenopathy tends to involve primarily the anterior cervical nodes overlying the sternocleidomastoid muscle [48]. Diffuse lymphadenopathy or other signs of reticuloendothelial involvement (eg, splenomegaly) should prompt a search for alternative diagnoses.

Children suspected of having KD who have fewer than four signs of mucocutaneous inflammation may have incomplete or atypical KD. Clinical manifestations of KD tend to be most incomplete and atypical in the youngest patients, and a particularly high level of suspicion is needed in infants younger than 1 year of age. In a retrospective review of 45 cases of KD, for example, 5 of 11 infants (45%) had atypical disease, compared with 4 of 33 older children (12%) [49]. Magnifying the gravity of the situation is the fact that infants are the group with the highest risk of developing coronary artery aneurysms. In the study by Joffe et al [49], coronary artery complications occurred in seven infants (64%) compared with three older children (9%) and occurred in all five infants with incomplete disease. Overall, among the 2221 children under 5 years of age analyzed for the Japanese nationwide survey of KD in 1995 and 1996, infants under 1 year of



Fig. 3. Periungual desquamation seen during the subacute phase of KD.

age had an odds ratio of 1.54 for developing cardiac sequelae [50]. Similarly, in a recent retrospective survey, the rate of treatment failure was 8.5% in patients under 12 months of age [51], compared with a 1.8% incidence of coronary artery abnormalities in those at least 12 months of age.

Thus, KD should be considered in any infant or young child with prolonged, unexplained fever. Although alternative explanations for the child's symptoms must be carefully excluded before instituting empiric treatment with intravenous immunoglobulin (IVIG), a high index of suspicion should be maintained for the diagnosis of incomplete disease. Consultation with an expert is recommended if the diagnosis is in question. Although no laboratory studies are included among the diagnostic criteria for KD, certain findings may help distinguish KD from mimics in ambiguous cases [44]:

- Systemic inflammation is most characteristic, manifested by elevation of acute-phase reactants (eg, CRP, ESR, and alpha-1 antitrypsin), leukocytosis, and a left shift in the white blood cell count. By the second week of illness, platelet counts generally rise and may reach  $1,000,000/\text{mm}^3$  in the most severe cases.
- Children with KD often present with a normocytic, normochromic anemia; hemoglobin concentrations more than two SD below the mean for age are noted in 50% of patients within the first 2 weeks of illness.
- The urinalysis commonly reveals white blood cells on microscopic examination. The pyuria is of urethral origin and therefore will be missed on urinalyses obtained by bladder tap or catheterization. In addition, the white cells are mononuclear and are not detected by dipstick tests for leukocyte esterase. Renal involvement may occur in KD but is uncommon.
- Measurement of liver enzymes often reveals elevated transaminase levels or mild hyperbilirubinemia caused by intrahepatic congestion. In addition, a minority of children develops obstructive jaundice from hydrops of the gallbladder.
- Other body fluids also demonstrate inflammation: cerebrospinal fluid (CSF) typically displays a mononuclear pleocytosis without hypoglycorrhachia or elevation of CSF protein. A chart review of 46 children with KD found that 39% had elevated CSF white cell counts; the median count was 22.5 cells with 6% neutrophils and 91.5% mononuclear cells, although cell counts as high as  $320/\text{mm}^3$  with up to 79% neutrophils were reported [52]. Similarly, arthrocentesis of involved joints demonstrates 50 to 300,000 white cells/ $\text{mm}^3$ , primarily consisting of neutrophils.

### *Differential diagnosis*

KD is most commonly confused with infectious exanthems of childhood [53]:

- Measles, echovirus, and adenovirus may share many of the signs of mucocutaneous inflammation, but they typically have less evidence of systemic inflammation and generally lack the extremity changes seen in KD.

- Toxin-mediated illnesses, especially beta-hemolytic streptococcal infection and toxic shock syndrome, lack the ocular and articular involvement typical of KD
- Rocky Mountain spotted fever and leptospirosis are two additional infectious illnesses to be considered in the differential diagnosis of KD. Headache and gastrointestinal complaints typically are prominent features of these infections.
- Drug reactions such as Stevens–Johnson syndrome or serum sickness may mimic KD but with subtle differences in the ocular and mucosal manifestations.
- Systemic-onset juvenile rheumatoid arthritis is marked by prominent rash, fever, and systemic inflammation and may be difficult to distinguish from KD until its chronicity and polyarthritis are evident.
- Mercury hypersensitivity reaction (acrodynia) shares certain clinical features with KD, including fever, rash, swelling of the palms and feet, desquamation, and photophobia. Unless there is a convincing history of exposure to mercury, however, treatment of a child with possible KD should not be delayed while awaiting mercury levels, because acrodynia is rare in the developed world.

## Therapy

Patients who fulfill the criteria for KD are hospitalized and treated with IVIG and aspirin. Patients suspected of having incomplete disease may require further testing such as slit-lamp examination and echocardiography to confirm the diagnosis. At times, children are treated for suspected KD when the diagnosis is uncertain but no clear alternative explanation for the clinical findings can be identified. Markers of increased risk of developing coronary artery aneurysms, including age under 1 year, signs of severe systemic inflammation (especially marked anemia and left shift in the white blood cell count), and a consumptive coagulopathy, may shift the balance toward empiric therapy [54].

Aspirin was the first medication used for treatment of KD because of its anti-inflammatory and antithrombotic effects [55]. Although aspirin was useful for management of fever and arthritis, it did not lower the incidence of coronary artery aneurysm development. A reduction in the occurrence of this complication was first reported with IVIG in 1984 [56]. IVIG offers a remarkable combination of efficacy and safety for the treatment of KD. Therapy within the first 10 days of illness reduces the incidence of coronary artery aneurysms by more than 70% [36]. IVIG therapy also largely eliminates the development of giant coronary artery aneurysms (more than 8 mm in diameter), which are associated with the highest risk of morbidity and mortality, and rapidly restores disordered lipid metabolism and depressed myocardial contractility to normal [45].

Aspirin traditionally is given initially in relatively high doses to achieve an anti-inflammatory effect; doses of 30 mg/kg/day to more than 80 mg/kg/day in

four divided doses have been used during the acute phase of illness. Subsequently, aspirin is administered in low doses (3 to 5 mg/kg/day) for its antiplatelet action. Alternative anti-inflammatory agents such as ibuprofen may be used for prolonged episodes of arthritis. No study has demonstrated long-term benefit from the use of aspirin, and a recent trial found no differences in outcomes between children treated with IVIG alone and those who also received aspirin [57]. In view of the potential risks and lack of obvious benefits of aspirin, it should be withheld in the presence of any contraindications to its use, including bleeding, exposure to influenza or varicella, or a history of hypersensitivity to salicylates. When used, the initial dose should be no higher than 100 mg/kg/day. Once fever resolves, patients receive a dose of 3 to 5 mg/kg/day. Treatment with aspirin is continued until laboratory studies (eg, platelet count and sedimentation rate) return to normal, unless coronary artery abnormalities are detected by echocardiography. This phase of therapy typically is complete within 2 months of the onset of disease.

Corticosteroids—prednisone and related medications—are mainstays of the therapeutic regimen in other forms of vasculitis, but they have been considered unsafe in KD. This conclusion is based primarily on a single study that demonstrated an extraordinarily high incidence of coronary artery aneurysms (11 of 17 patients) in a group that received oral prednisolone at a dose of 2 to 3 mg/kg/day for at least 2 weeks, followed by 1.5 mg/kg/day for an additional 2 weeks [58]. These data are difficult to interpret, because treatment groups were not stratified according to risk factors for the development of aneurysms, and no information about randomization methods was given. In addition, a smaller group of seven patients in the same study received prednisolone plus aspirin, and none of these patients developed aneurysms.

A detrimental effect of steroids in patients with vasculitis would be unprecedented, and several recent reports have rekindled interest in a possible role for steroids in the management of KD. A retrospective survey of the records of almost 300 children treated with or without steroids between 1982 and 1998 [59] and two open, randomized, prospective trials [60,61] found that patients who received corticosteroids in addition to IVIG had shorter durations of fever and more rapid decrease in inflammatory markers than those in the standard-therapy group. In all reports, corticosteroid therapy has been well tolerated, with no significant adverse effects. At present, most clinicians who specialize in the care of KD use pulsed doses of intravenous methylprednisolone (IVMP) in children whose inflammation persists despite at least two doses of IVIG [51]. A trial supported by the National Institutes of Health comparing outcomes in children who received initial therapy with IVMP plus IVIG versus IVIG alone has completed enrollment. Results of this trial soon should supply definitive information concerning the potential role of steroids in the primary treatment of KD.

### *Re-treatment*

Fever persists or returns 48 hours after the start of initial treatment with IVIG in 10% to 15% of patients [62]. Persistent or recrudescing fever is particularly

concerning, because it usually indicates ongoing vasculitis with increased risk of developing coronary artery aneurysms (12.2% versus 1.4% in one analysis) [54]. In another study, persistent fever was the only factor that predicted subsequent development of aneurysms [37]. Thus, it is extremely important not to dismiss mild temperature elevations in children with KD; one should assume that these elevations represent incompletely controlled disease unless proved otherwise. Patients who remain febrile after the first dose of IVIG are usually treated with a second and perhaps even a third dose of IVIG, 2 g/kg [51]. This practice is based on the apparent dose–response effect of IVIG [63]. Nonetheless, children are not usually re-treated until at least 48 hours after the start of the initial IVIG infusion, because fever before this time may represent a reaction to the medication.

A subgroup of patients with KD seems to be resistant to IVIG therapy, even after multiple doses. These patients are at greatest risk for development of coronary artery aneurysms and long-term sequelae of the disease. Therapies that are effective in other forms of vasculitis, such as corticosteroids, pentoxifylline, plasmapheresis, and immunosuppression, have been used in these patients. Prospective studies have not compared these options, but most specialists treat children who have not responded to IVIG and still have active KD with one to three daily doses of pulsed methylprednisolone (30 mg/kg) [51]. If this treatment is ineffective, a single dose of infliximab, 5 mg/kg, may be beneficial [64].

The need for more potent immunosuppressive agents (eg, cyclophosphamide or cyclosporine) in KD is not clear. These medications are relatively toxic, with delayed onsets of action. Because fever generally lasts less than 3 weeks even in the most severe cases of KD, few patients will remain sick enough to consider immunosuppression by the time routine therapies have been exhausted. When symptoms are prolonged beyond 3 to 4 weeks, consideration should be given to an alternative diagnosis, including chronic vasculitides such as PAN.

### *Additional considerations*

An echocardiogram should be obtained early in the acute phase of illness and 6 to 8 weeks after onset to confirm the efficacy of treatment [38]. Patients should also have repeated physical examinations during the first 2 months to detect arrhythmias, heart failure, valvular insufficiency, or myocarditis. Children with coronary artery abnormalities generally receive long-term antithrombotic therapy with aspirin, dipyridamole, or other agents, as well as regular cardiac evaluations.

Coronary artery dilatation of less than 8 mm generally regresses over time, and most smaller aneurysms fully resolve by echocardiogram [65]. Healing is by fibrointimal proliferation, often accompanied by calcification, and vascular reactivity does not return to normal despite grossly normal appearance [66]. Children should thus be followed indefinitely after KD, a point highlighted by a report of the sudden death of a 3.5-year-old child 3 months after dilated coronary arteries had regained a normal echocardiographic appearance [67]. Autopsy revealed obliteration of the lumen of the left anterior descending coronary artery by fibrosis, with evidence of ongoing active inflammation in the epicardial arteries.

Children with severe KD who develop coronary occlusion may experience myocardial infarction, arrhythmias, or sudden death, and those who develop peripheral artery occlusion may experience ischemia or gangrene [68]. Various therapies have been attempted to restore circulation, although control of vascular inflammation with sufficient IVIG or corticosteroids is an essential prerequisite to arterial reperfusion. Thereafter, treatments may include thrombolytic therapy, if arterial thrombosis is present, or vasodilators, if tissue viability is threatened primarily by vasospasm.

At least one report suggests a potential role for abciximab, a monoclonal antibody that inhibits platelet glycoprotein IIb/IIIa receptor [69]. A group from the University of Utah reported increased resolution of aneurysms in patients with KD who received abciximab compared with those who received conventional treatment. Subsequent case reports have been less promising, however.

Overall, with modern treatment and cardiologic follow-up, the prognosis of children with KD is excellent. Long-term follow-up of children without persistent coronary artery abnormalities in Japan has demonstrated no increase in morbidity or mortality after 25 years [70]. In fact, studies suggest that fear of a cardiac event is more disabling than actual medical problems in most children who have had KD [71]. Thus, caregivers should be particularly careful to reassure families when appropriate.

### **Polyarteritis nodosa**

PAN is a systemic necrotizing vasculitis with aneurysm formation affecting medium or small arteries. This condition is important historically as the first noninfectious cause of vascular damage to be identified. In 1866, Kussmaul and Maier's extensive report described a 27-year old tailor with diffuse visceral involvement as well as features of systemic inflammation (fever, fatigue, weight loss). At least one third of children with PAN, however, have a more limited form, restricted largely to the skin and joints.

Worldwide, PAN is most commonly associated with hepatitis B or C infections [72]. Perhaps because of the relative infrequency of these infections in children, pediatric PAN is quite rare, especially in North America. When it does occur before adulthood, PAN incidence peaks at 9 to 10 years of age, and it may be slightly more common in boys than in girls [14]. No clear genetic association has been identified, although several reports suggest an association with familial Mediterranean fever (FMF). Up to 1% of FMF patients develop PAN, but in these patients it seems to be milder than idiopathic disease and is associated with a better prognosis [73].

Cutaneous PAN is usually limited to skin and the musculoskeletal system. It commonly occurs after a sore throat or streptococcal pharyngitis. Livedo reticularis, maculopapular rash, painful skin nodules, panniculitis, brawny edema, and arthritis mostly affect the knees and ankles [74]. Acute-phase reactants may be normal or elevated, at least partially reflecting the severity of the inciting

infection [75,76] Constitutional symptoms are generally mild. Even though systemic involvement is quite rare, these patients should be observed closely for development of systemic disease. Symptoms are more troubling than disabling, and treatment generally consists of NSAIDs and steroids. The disease does tend to persist or relapse, so many patients require steroid-sparing agents for long-term management. These drugs may include methotrexate or other immunosuppressive agents; TNF inhibitors have been reported to be effective, as well [77]. Penicillin prophylaxis may prevent disease flares caused by recurrent streptococcal infections.

Systemic PAN may involve virtually any muscular artery. Consequently, in addition to constitutional symptoms, it may cause a vast array of organ dysfunction. Palpable purpura, livedo, necrotic dermal lesions (Fig. 4), abdominal pain, arthritis/arthralgia, myositis/myalgia, renovascular hypertension, neurologic deficits, pulmonary disease, and coronary arteritis may be seen at presentation or during the course of the disease, so PAN should be considered in the differential diagnosis of any undiagnosed systemic inflammatory condition [78]. Because of its pleomorphism, PAN may be confused with systemic-onset juvenile rheumatoid arthritis, KD, or dermatomyositis. Small vessels are spared in classical PAN, however, so glomerulonephritis typically is not a feature of this condition.

Laboratory evaluation usually reflects the ongoing systemic inflammation including anemia, leukocytosis, thrombocytosis, and elevated ESR, CRP, and immunoglobulins. A positive ANCA generally indicates pauci-immune glomerulonephritides rather than PAN. Proteinuria, hematuria, and increases in serum urea nitrogen and creatinine levels are also common findings. Complement levels are normal. The diagnosis usually requires tissue biopsy or radiologic documentation of vasculitis. Imaging studies demonstrate the typical beading of vessels caused by alternating areas of vascular narrowing and dilatation that give PAN its name. Pathologically this manifestation corresponds to segmental vascular involvement with nodule and aneurysm formation resulting from panmural fibrinoid necrosis. No overt complement or immunoglobulin deposition is seen.

Treatment usually aims at decreasing systemic vascular inflammation, mainly with high-dose steroids. Other immunosuppressive agents, primarily daily oral



Fig. 4. Ulcerating livedo reticularis characteristic of polyarteritis nodosa.

or monthly intravenous doses of cyclophosphamide, seem to be beneficial in improving outcome. Azathioprine, methotrexate, IVIG, and, more recently biologic response modifiers such as TNF-inhibitors, have been used in a number of patients. Randomized, controlled trials are needed to determine the most effective remittive and maintenance therapies as well as predictors of individual patients' responses. Nonetheless, recent reviews of PAN in children suggest an excellent overall prognosis, with a 4-year mortality rate under 5% [14].

### **Takayasu arteritis**

TA is the third most common form of childhood vasculitis [79]. The cause of TA remains unknown, although histopathology and immunohistochemistry of biopsy and autopsy samples from adults with TA suggest a primarily T-cell-mediated mechanism [80]. Pathologically TA lesions consist of granulomatous changes progressing from the vascular adventitia to the media, indistinguishable from those seen in giant cell arteritis and temporal arteritis [81]. The diagnosis of TA is based on the distribution of involvement—primarily the aorta and its branches—and the young age of patients, typically under 40 years. TA is more common in the Far East and West Africa than in Europe and North America. Certain HLA associations have been found in Japan, but these have not been confirmed in other populations [82].

Onset of TA is most commonly during the third decade of life, but childhood disease has been reported as early as the first year of life [75]. As in adults, there is a significant preponderance of female patients in children with TA, and the distribution of vessel involvement parallels that in adults as well, with diffuse aortic involvement predominating. In a recent review of childhood TA, the mean age of onset was 11.4 years, and two thirds of the patients were female [83]. Signs and symptoms included hypertension, cardiomegaly, elevated ESR, fever, fatigue, palpitations, vomiting, nodules, abdominal pain, arthralgia, claudication, weight loss, and chest pain. The delay in diagnosis in children was 19 months, notably longer than that reported in most adult series [84]. Possibly because of delayed diagnosis, mortality was 33%, also significantly higher than reported in adult series.

Once TA is suspected, angiography has been the standard method used for diagnosis. The size of the vessels involved and the spotty nature of the vascular inflammation make biopsies impractical. In recent years, CT and MR angiograms have proven to be as useful as traditional angiograms and far less invasive. MRI has the added advantage of revealing evidence of ongoing vessel wall inflammation. This information is particularly helpful because of the need to suppress the vasculitis completely to prevent disease progression. Laboratory markers may be entirely normal despite ongoing inflammation, so MRI offers a potentially more sensitive test for residual disease [85].

As with all vasculitides, early diagnosis and aggressive therapy are important in TA to prevent irreversible vessel damage with resulting compromise of vital

organs. Steroids and the typical immunosuppressive agents used in other vasculitides (including cyclophosphamide, methotrexate, and azathioprine) have shown variable efficacy in TA. A recent report in adults with TA from the Cleveland Clinic documented a high response rate to TNF-inhibitors [3]. Before starting such treatment, however, it is important to test patients for tuberculosis, because aortitis is associated with mycobacterial infections, especially in less developed countries [86].

### **Primary angiitis of the central nervous system**

Primary angiitis of the central nervous system (PACNS) is potentially one of the most challenging diseases a physician might face, both diagnostically and therapeutically [87]. By definition, systemic manifestations of the disease are usually absent, acute-phase reactants are typically normal, and examination of CSF might be unrevealing as well [88]. Thus, to make the diagnosis before the patient comes to autopsy, clinicians must have a high level of suspicion when children have even scanty suggestion of a vasculitis. A recent review based on 62 patients with childhood PACNS (cPACNS) helps shed light on symptoms that might suggest inclusion of PACNS in a child's differential diagnosis [89]. Headache (80%) and focal neurologic deficits (78%) were the most common presenting complaints, followed by hemiparesis in 62%. When a clearly defined infectious, toxic, or vascular abnormality cannot account for such findings, brain and cerebral vessel imaging are indicated. Normal MRI together with normal CSF have high negative predictive value for cPACNS. Nonetheless in 5% to 10% of cases of cPACNS, only a meningeal and brain biopsy, guided by clinical or MRI abnormalities or performed blindly, reveals diagnostic evidence of the vasculitis.

Although brain biopsy remains the reference standard for the diagnosis of cPACNS, even these results may be falsely negative because of the patchy nature of the disease. Biopsy is also useful in excluding mimics of CNS vasculitis, especially atypical infections that could worsen if immunosuppressive therapy is started empirically. PACNS may be rapidly progressive and neurologically devastating, so the risks of diagnostic procedures must be weighed against the need for prompt diagnosis and initiation of therapy. Treatment invariably includes corticosteroids and a potent immunosuppressive agent, usually cyclophosphamide. Outcomes using these agents to achieve initial disease control, followed by methotrexate or azathioprine for maintenance therapy, are excellent [89].

### **Anti-neutrophil cytoplasmic antibody-associated vasculitides**

#### *Wegener's granulomatosis*

Wegener's granulomatosis (WG) is uncommon in children. It is a necrotizing granulomatous inflammation of small- to medium-sized vessels involving the

kidneys and upper and lower respiratory tracts. As with other ANCA-associated vasculitides, biopsies of active lesions reveal a microscopic pauci-immune polyangiitis. Serologic testing is positive for cANCA directed against PR-3. Available data suggest that clinical manifestations in children are similar to those in adults [90]. In a recent report of 17 children, nasal and sinus involvement were seen in 100%, respiratory disease in 87%, arthralgias, ocular findings, or skin or renal involvement each in just over 50%, gastrointestinal disease in 41%, and CNS involvement in 12% [91]. In this and other pediatric series, subglottic stenosis has been more frequent than in adults, noted in almost 50% of children with WG.

Although the cause of WG remains unknown, pathogenesis seems to be related to ANCA. ANCA most likely stabilize adherence of rolling neutrophils to endothelium and activate neutrophils and monocytes to undergo an oxidative burst. Activation of phagocytic cells causes increased expression of proinflammatory cytokines (eg, TNF- $\alpha$  and IL-8), with resultant localized endothelial cell cytotoxicity [11].

Most children with WG present with upper respiratory symptoms such as epistaxis, sinusitis, otitis media, or hearing loss. Cough, wheezing, dyspnea, and hemoptysis are among the lower respiratory tract manifestations. Because benign causes of these symptoms are so much more prevalent than WG in children, these patients usually are treated for infections or allergies. Further, despite the potential severity of the glomerulonephritis seen in WG, kidney involvement may initially be asymptomatic. Thus, as with other rare conditions, pediatricians must remember to consider WG in a child with respiratory disease that is unusually persistent or severe. Chest radiographs may be particularly helpful when a diagnosis of WG is suspected, because even in asymptomatic children up to one third have radiographic abnormalities.

Confirmation of a diagnosis of WG relies heavily on biopsy results. Necrotizing granulomatous vascular inflammation is strongly suggestive in a child with consistent clinical features. cANCA targeted against PR-3 is positive in most patients [92]. Although this autoantibody is highly specific, it may be found in other diseases, such as cystic fibrosis, which are more common in children. Accordingly, a positive ANCA titer should not replace a tissue biopsy in confirming the diagnosis of WG, nor should ANCA screening substitute for a careful history and physical examination. The role of monitoring of ANCA titers as a marker of disease activity is also controversial. Some studies have shown a correlation between rising ANCA titers and relapses of WG, whereas others found no correlation [93]. Currently, intra- and interpatient variability in antibody titers means that treatment of anticipated relapses based on rising ANCA titers alone is not generally recommended.

Without effective immunosuppressive therapy, WG is commonly rapidly progressive and even fatal. Current therapeutic practices reflect this potential, relying on potent combination therapies including steroids, cyclophosphamide, azathioprine, methotrexate, and, more recently, mycophenolate mofetil and TNF- $\alpha$  blockers. Preliminary data showed that the anti-TNF agent etanercept did

not prove effective in adults with WG, but infliximab apparently was effective [4]. It is not clear whether this finding represents a fundamental difference in the agents or simply different potencies, but it does highlight the need for cooperative studies of new agents in the treatment of rare diseases, rather than haphazard experimentation by individual practitioners.

Despite progress in the management of WG, the disease continues to cause significant morbidity and mortality from relapses and treatment-related toxicity. Subglottic stenosis does not respond to systemic therapy but requires surgical dilatation and local steroid injections. In patients with limited upper respiratory disease, trimethoprim/sulfamethoxazole has been shown to be beneficial [94], perhaps by suppressing upper respiratory infections that might activate vascular inflammation.

### *Microscopic polyangiitis*

Microscopic polyangiitis is a necrotizing vasculitis of the small vessels without granuloma formation. Clinical manifestations typically center around kidney and pulmonary involvement, especially focal segmental glomerulonephritis and pulmonary hemorrhage. The disease is characterized by a positive pANCA with reactivity to myeloperoxidase (MPO) by immunoblotting. In fact, these auto-antibodies seem to be integral to disease pathogenesis, activating neutrophils whose cytotoxic granules cause local vascular damage [95]. Thus, one must be cautious about making the diagnosis of microscopic polyangiitis in the absence of a positive ANCA. Biopsy or radiographic confirmation of vascular inflammation is also necessary to confirm the diagnosis, however, because nonspecific ANCA may be seen in a variety of other conditions, including inflammatory bowel disease, primary sclerosing cholangitis, and silicosis.

A diagnosis of microscopic polyangiitis seems to identify a disease with a severe and chronic course and significant risk of chronic renal failure. Most patients seem to require cyclophosphamide to achieve disease control. Milder agents may be adequate for maintaining remissions [96]. Most recently, a small, uncontrolled series suggested that a single 4-week course of rituximab might replace both cyclophosphamide and long-term steroids [5]. Larger studies aimed at confirming this finding will begin enrolling patients shortly.

### *Churg–Strauss syndrome*

CSS is extremely rare in children. The first report of this small-vessel disease of the lungs, skin, peripheral nerves, heart, and gastrointestinal tract occurring in a preteen-aged child was made only in the past decade. The prodromal phase of CSS is manifested only as allergic rhinitis and asthma, and it may persist for many years. The second phase is characterized by worsening asthma, peripheral eosinophilia, and pulmonary infiltrates. Only during the third or vasculitic phase

do manifestations of systemic vasculitis become evident, with weight loss, fever, arthralgia, myalgia, nodular rash, and neuropathy. Asthma symptoms usually subside during the vasculitic phase. In some cases, it may be difficult to differentiate CSS from PAN, although in CSS renal hypertension and nephritis are uncommon, and peripheral eosinophilia is quite striking. Tissue biopsy is generally diagnostic, with significant perivascular eosinophilic infiltrates and occasional extravascular granulomas. ANCA directed against both PR-3 and MPO may be seen in CSS.

The optimal regimen for treating CSS is not clear, although an initial aggressive remittive therapy, followed by milder maintenance treatment, may offer the best combination of safety and efficacy [96]. Disease control is necessary because untreated CSS is usually progressive. Most deaths are caused by cardiac involvement, followed by severe gastrointestinal and CNS disease. Fortunately, because CSS is exquisitely sensitive to corticosteroids, they offer a good bridging therapy until effects of remittive agents become evident.

## Secondary vasculitides

Vasculitis may occur in the setting of a wide variety of infections, medications, and systemic diseases. These settings seem to represent a heightened susceptibility to vascular inflammation, because most people exposed to these viruses (parvovirus B19, HIV, varicella), Rickettsia, bacteria, fungi, mycobacteria, systemic inflammatory conditions (systemic lupus erythematosus, juvenile dermatomyositis [JDMS], juvenile rheumatoid arthritis, sarcoidosis, inflammatory bowel syndrome, tumors) and drugs (including leflunomide, TNF inhibitors, and anti-thyroid agents) do not develop vasculitis. Both leukocytoclastic and necrotizing vasculitis have been reported [97]. In most cases, removal of the trigger or control of the inciting condition leads to remission of the vasculitis.

### *Behçet's disease*

Behçet's disease (BD) is a multisystem inflammatory disorder with manifestations similar to those of spondyloarthropathies. BD is characterized by the triad of recurrent oral ulcers, genital ulcers, and uveitis, but any organ system may be involved including skin, joints [98], CNS, or gastrointestinal tract, and vascular inflammation is often a prominent feature. Both arteries and veins may be affected, but there seems to be a particular predilection for the venules. Also characteristic of BD is a propensity for development of thromboses, including deep vein thrombosis and thrombophlebitis. Arterial aneurysms may also occur, and pulmonary aneurysms are a significant cause of mortality [99].

BD is thought to occur when an infectious agent triggers an amplified inflammatory response in a genetically susceptible host. In the Japanese and Turk-

ish populations, in whom the disease is most prevalent, HLA-B51 is a marker for BD [100], and the aberrant cellular immune response seems to involve  $\gamma\delta$ -T cells. Antibody-mediated immune mechanisms may also play a role, given the cases of transient neonatal BD apparently caused by transplacental passage of antibodies from affected mothers. Various immunomodulatory agents, including IFN- $\alpha$ , thalidomide, and dapsone, are effective in some cases of BD, as are a variety of immunosuppressive agents, such as steroids, cyclophosphamide, and azathioprine [101]. The prognosis of BD seems to be worse in young males. Overall, the disease is less severe in Western countries.

### *Periodic fever syndromes*

During the past 5 years, novel autoinflammatory conditions caused by mutations in regulators of inflammation have been described. As these periodic fever syndromes have been further characterized, an association with vasculitis has come to light. The gene defect responsible for FMF, a dysfunctional mutation of the protein pyrin, predisposes carriers to the development of HSP and PAN [102]. A group from Germany recently reported a small-vessel vasculitis in a patient who was found to have another periodic fever syndrome caused by the TNF receptor-associated periodic syndrome mutation [103]. They hypothesize that abnormal metabolism of TNF in this patient led to premature leukocyte activation and endothelial damage. The extent to which similar abnormalities in regulators of inflammation may account for other cases of vasculitis remains unknown, but these discoveries have opened new avenues of investigation into the pathogenesis of systemic vascular diseases.

## **Summary**

Vasculitis is rare in children, and, apart from HSP and perhaps KD, most practicing pediatricians will never encounter a case. Nonetheless, progress in the diagnosis and treatment of these conditions has afforded most children with vasculitis a reasonably good prognosis. Accordingly, it is important to consider vasculitis as a potential cause of unexplained inflammation, perplexing rashes, or strange combinations of symptoms. Although evaluation and management of suspected vasculitis are difficult in the best of situations, they are impossible if the diagnosis is not considered.

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