Polyarteritis Nodosa

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Polyarteritis (or periarteritis) nodosa is an uncommon form of vasculitis characterized by widespread necrotizing inflammation of medium and small arteries. The process usually involves adjacent veins as well and sometimes arterioles and venules, but never capillaries. Though the cause is not known with certainty, autoimmunity is thought for several reasons to be responsible. Vasculitis is a known manifestation of serum sickness and is commonly observed in immune-complex diseases, both natural and experimentally induced. Furthermore, antibodies and complement components can often be identified histochemically in the lesions of various types of vasculitis. In the case of polyarteritis nodosa specifically, a possible association with the hepatitis-associated antigen is suggested by findings that nearly half the patients with the disease have the antigen in their sera and have vascular lesions containing the antigen along with immunoglobulins and complement.

Pathology

The characteristic necrotizing angiitis is segmental in nature, sometimes affecting only a portion of the vessel circumference, and has a predilection for artrial bifurcations. These weakened areas tend to form small aneurysms, which may rupture, and when located subcutaneously represent the "nodules" that form the basis of the name.

Acute lesions demonstrate edema and fibrinoid necrosis of the media with polymorphonuclear leukocytic and some eosinophilic infiltration of the involved vessel wall and adjacent perivascular space. Thrombosis and infarction or hemorrhage may occur at this stage. Later, the infiltrate shifts gradually to one of the mononuclear cells, and the areas of necrosis are replaced by cellular granulation tissue. Finally comes replacement of the areas of necrotizing inflammation with scar tissue and associated intimal thickness and perivascular fibrosis. Occlusion may occur during either the acute or the chronic stage from vessel wall edema or obliterative proliferation, respectively. A characteristic feature is the coexistence, often within adjacent sections of a vessel, of acute and chronic changes, suggesting a continuous process with repeated insults. A number of the histopathologic features are illustrated in Figure 1.

Commonly affected organs include the heart, the intestinal tract, the kidney, and muscle. Central nervous system involvement is unusual, and rarely is the lung affected.

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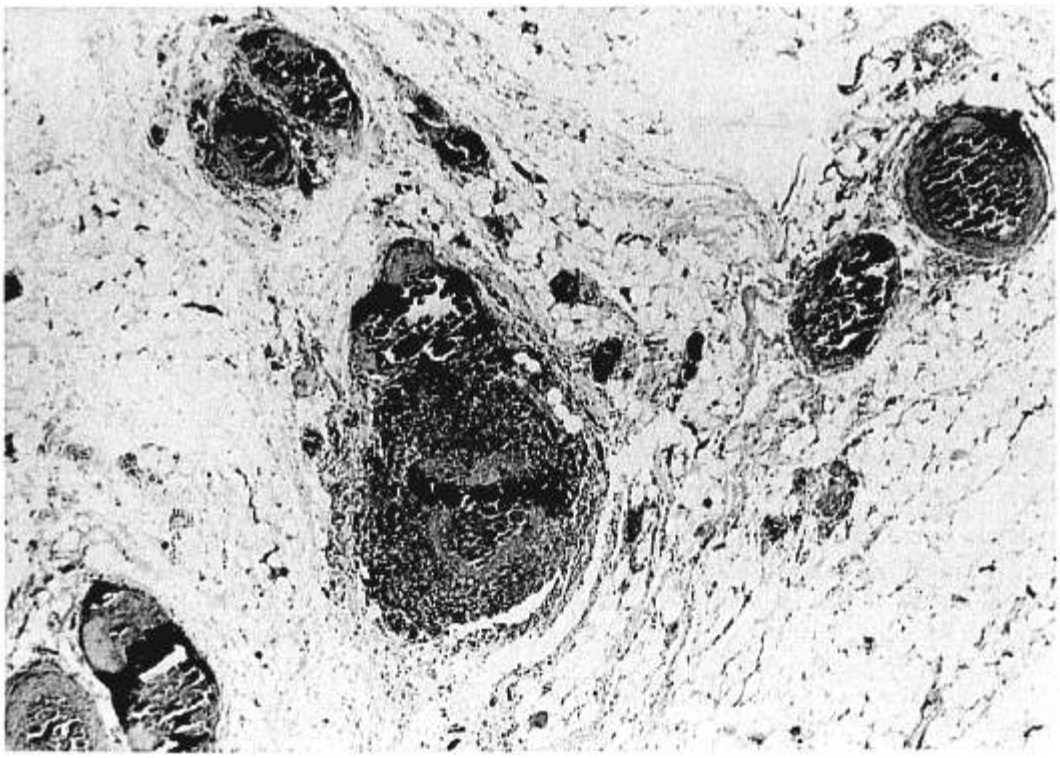

FIG. 1. *Photomicrograph of mesenteric vessels from fatal case of polyarteritis nodosa demonstrating necrotizing arteritis (center) and adjacent normal vessels. (Courtesy of Dr. Jo A. Benda.)*

Clinical Manifestations

The age of affected individuals varies widely. There is a peak incidence in the 5th and 6th decades. Men outnumber women by two or three to one.

The onset may be either acute or insidious. As indicated in Table 1, early symptoms are typically generalized and nonspecific, such as fever, weakness, anorexia, weight loss, myalgia, and arthralgia. The occurrence and location of any localizing symptoms seem to depend on the areas of involvement. Abdominal complaints are frequent, consisting of pain, nausea, diarrhea, and bleeding, all apparently reflecting involvement of the mesenteric arteries. Involvement of the biliary tree may lead to massive hepatic infarction or cholecystitis with perforation. When the abdominal symptoms are acute and severe, as they often are, an intraabdominal catastrophe must be considered, and laparotomy is occasionally indicated.

TABLE 1. Clinical Manifestations of Polyarteritis Nodosa

Fever	80%
Leukocytosis	70%
Albuminuria	65%
Edema	52%
Neuritis	48%
Hematuria	47%
Hypertension	46%
Weakness	41%
Vomiting	31%
Arthritis	27%
Purpura	22%
Nodules	16%

From Harris et al.[1]

The kidneys are affected in over half the patients with arterial and arteriolar involvement leading to glomerulosclerosis. Hypertension, along with renal failure, frequently results. However, hypertension may also be found early in the disease when there is no

demonstrable renal disease. Cardiac involvement occurs fairly commonly. Pericarditis, with or without effusion, may be seen, and affected coronary arteries may lead to myocardial infarction. Other areas of clinical involvement depend on the location of the widespread vascular lesions. Occlusion of digital arteries can cause ulceration and gangrene of the fingers and toes. Retinal hemorrhages and exudates may be observed, and involvement of the vasa nervorum may lead to symptoms and findings suggesting polyneuritis.

The prognosis of polyarteritis nodosa, particularly with multisystem involvement, is grave. In untreated patients, half or more die within a year, although treatment undoubtedly affords some improvement in these grim statistics. Hypertension and/or renal disease seem to be especially serious prognostic signs. The causes of death include renal failure, myocardial infarction, congestive heart failure, and gastrointestinal bleeding.

Diagnosis

There is no specific laboratory test for polyarteritis nodosa. More than 75% of patients, at least those with acute symptomatology, exhibit leukocytosis (reflecting neutrophilia) and elevation in the erythrocyte sedimentation rate. Anemia may be present, usually because of blood loss, but occasionally hemolytic in origin. Other laboratory findings depend on the nature of involvement—hematuria, proteinuria, and other urinary abnormalities if the kidney is affected, electrocardiographic changes if vasculitis involves the coronary arteries, et cetera.

Angiography may be helpful in establishing the diagnosis by demonstrating the characteristic aneurysms at arterial bifurcations in the kidney, mesentery, liver, pancreas, and other involved organs. Usually, however, the diagnosis is difficult and must be made presumptively on clinical grounds in a patient with symptoms and signs pointing to a multisystem disease. The presence of fever along with somewhat vague generalized complaints (lethargy, myalgia, arthralgias) may initially suggest a influenzalike syndrome. Tender subcutaneous nodules, though present in only a minority of cases, are helpful when found. Among diseases to be excluded are infections (particularly of the chronic granulomatous type), lymphomas, systemic lupus erythematosus, and other vasculitis syndromes such as allergic angiitis and Wegener's granulomatosis.

In establishing a diagnosis histopathologically, biopsies should be performed at clinically involved areas such as painful nodules, tender muscles, or infarcted skin. Thorough examination for the characteristic spectrum of effects of acute and chronic vasculitis is essential because of the scattered and segmental nature of involvement.

Treatment

The introduction of corticosteroids into the therapy of polyarteritis nodosa 30 years ago improved the grim prognosis of the disease. A review of the Mayo Clinic experience[2] noted a 5-year survival of 48% with adrenocorticotropic hormone (ACTH) or glucocorticoid (usually cortisone) treatment, compared with one of 13% in untreated cases. The contemporary approach involves prednisone, in initial doses of 40-60 mg daily, tapered gradually to the lowest dose providing control of the signs and symptoms, with long-term maintenance at this level.

More recently, immunosuppressive-cytotoxic therapy has been incorporated into the therapeutic regimen, an addition that seems to have further improved the results. Leib and associates[3] analyzed retrospectively a series of 64 patients seen between 1955 and 1977; and the results, summarized in Table 2, seem to indicate a benefit from immunosuppressive agents (usually azothioprine) combined with steroids. Further evidence of a beneficial effect of immunosuppressive agents comes from a recent report[4] of 17 patients with severe systemic vasculitis, all but one nonresponsive to high-dose corticosteroid therapy. Treatment with cyclo-

TABLE 2. Treatment of Polyarteritis Nodosa

Therapy	Median Survival	5-year Survival
Supportive only (n = 8)	3 mo.	12%
Steroids alone (n = 34)	63 mo.	53%
Steroids and immunosuppressives (n = 22)	149 mo.	80%

From Leib et al.[3]

phosphamide (or in one case azothiaprine) at doses of 2 mg/kg per day induced complete and often dramatic remission, which persisted throughout cytotoxic therapy, even in some cases when corticosteroids were discontinued.

Cutaneous Periarteritis Nodosa

The foregoing discussion relates to a widespread multisystem disease that is severe and often fatal. In contrast are reports, appearing mainly in the dermatologic literature, of a condition in which the symptoms and findings are limited largely or entirely to the skin. Some regard this "cutaneous periarteritis nodosa" as a form or a stage of the more florid disease, whereas others argue that it is an entirely different entity characterized by localized cutaneous vascular changes and a chronic, protracted, and benign course that never seriously compromises the health of the patient. The former view is supported by Fisher and Orkin,[5] who concluded from an experience with three cases that the only difference between the systemic and cutaneous forms was the duration of the disease. These authors suggested that the principal determinant was the degree of visceral involvement. When severe, progress is rapid and earlier death results; whereas when minimal, the cutaneous component has time to develop. Diaz-Perez and Winkelmann,[6] on the other hand, noted that none of their 23 patients with skin biopsies demonstrating periarteritis died and instead followed a prolonged and essentially asymptomatic course; these authors concluded that cutaneous periarteritis is an entity distinct from the systemic disease, the relationship between them analogous to that between discoid and disseminated lupus erythematosus.

Polyarteritis and Pregnancy

As noted previously, polyarteritis nodosa is an uncommon disease with peak incidence around the 5th decade and male preponderance. Not surprisingly, therefore, it represents an extremely rare complication of pregnancy. In fact, the literature contains only 10 reported cases. These 10 cases are summarized in Table 3.

Literature Review

Webb[7] reported the first case of polyarteritis nodosa in pregnancy in 1944. The patient presented with acute symptoms and signs of severe preeclampsia at 34 weeks. Labor was induced, and the patient died on the 4th postpartum day. The diagnosis of polyarteritis nodosa was made at autopsy. Chesley reported two separate cases, both in 1949. The first[8] was a patient known to be hypertensive for 5 years whose blood pressure increased markedly during the first trimester of pregnancy. A therapeutic abortion was done at 18 weeks for "malignant hypertension," but the patient died in uremia 42 days later. The autopsy indicated both "malignant nephrosclerosis and polyarteritis nodosa," though now it seems likely that the latter was the primary lesion. Chesley's second case[9] was that of a relatively uncomplicated pregnancy with what was thought to be either cardiac failure or pulmonary embolism during the early puerperium and a respiratory type of death on the 7th postpartum day. Autopsy revealed "arteriolitis of lungs with periarteritic nodules of granulation" along with endocarditis, myocarditis, and pericarditis. This case has been included in earlier reviews of polyarteritis in pregnancy, but its inclusion seems questionable.

Tait's case[10] reported in 1949 was that of persistent and obscure postpartum fever with development of gastrointestinal symptoms, mental confusion, parethesia, and, ultimately, renal failure. A diagnosis of

TABLE 3. Polyarteritis Nodosa and Pregnancy: Summary of Reported Cases

References	Onset of Disease		Diagnosis	Treatment	Delivery	Outcome	
	Timing	*Clinical Picture*				*Mother*	*Infant*
Webb[7]	Third trimester	"Toxemia" near term	Autopsy	Induction	Vaginal	Died 4 days after delivery	Liveborn at 35 weeks
Chesley[8]	First trimester	Marked worsening of hypertension at 10–15 weeks	Autopsy	Therapeutic abortion	Induced abortion	Died in uremia 42 days after abortion	Abortion at 18 weeks
Chesley[9]	Early puerperium	Dyspnea and cyanosis	Autopsy	Anticoagulation	Vaginal	Died in respiratory failure 7 days after delivery	Liveborn at 36 weeks
Tait[10]	Early puerperium	Fever, diarrhea, mental disturbance	Autopsy	Antibiotics, ACTH	Vaginal	Died in coma 40 days after delivery	Liveborn
Siegler and Spain[11]	34 weeks	"Eclampsia"	Autopsy	$MgSO_4$, delivery	Cesarean	Died with GI hemorrhage 15 days after delivery	Liveborn at 34 weeks
Varriale et al.[12]	30 weeks	Hypertension and cardiac failure	Autopsy	Symptomatic	Vaginal	Died in coma 33 days after delivery	Liveborn at 32 weeks
Szinnyai et al.[13]	8 years prior to pregnancy	"Toxemia" near term	Prepregnancy	Steroids	Cesarean	Survived	Fetal death
DeBeukelaer et al.[14]	4 years prior to pregnancy	In remission	Prepregnancy	Steroids	Vaginal	Survived	Liveborn at 34 weeks
Reed and Smith[15]	First trimester	Hypertension, RUQ pain	Prenatal	Steroids	Spontaneous abortion	Died in uremia at 22 weeks	Abortion at 20 weeks
Burkett and Richards[16]	2 years prior to pregnancy	Hypertension, edema, and proteinuria in third trimester	Prenatal	Steroids induction	Vaginal	In remission until 18 months postpartum when died in renal and cardiac failure	Liveborn at 37 weeks

periarteritis nodosa was made on clinical grounds 37 days postpartum, and ACTH therapy was begun, but the patient died 3 days later. Autopsy confirmed widespread involvement (lungs, heart, adrenals, and kidneys) with periarteritis nodosa. Siegler and Spain[11] in 1961 described a woman with eclampsia at 34 weeks who remained comatose for 2 weeks after cesarean delivery and then died suddenly with massive gastrointestinal hemorrhage on postpartum day 19. The patient described by Varriale and colleagues[12] presented with hypertension and cardiac failure, thought to be eclamptic in origin, in the early third trimester and died in coma during the puerperium.

The case reported by Szinnyai and associates[13] in 1970 has received no previous note in the English language literature, probably because it appeared in an East German publication. The patient was a 26-year-old nullipara in whom polyarteritis nodosa was diagnosed histologically 8 years prior to pregnancy. For most of the course of her disease, only skin symptoms were present. However, during gestation she developed increasingly severe systemic manifestations and, in addition, a diagnosis of toxemia of pregnancy was made near term. The fetus died antepartum, and delivery was accomplished by cesarean section, which was associated with marked postpartum improvement in the patient's condition. This case is interesting for several reasons. It is the first reported instance of maternal survival and the only time in which the death of a viable fetus has been recorded. Additionally, it contains the only description of the placenta in polyarteritis nodosa: "Extensive white infarcts were seen on the placenta. The microscopic examination showed chorion with necrosis and a high degree of syncytiotrophoblastic growth. The intervillous space was restricted by fibrinoid substance. The endarteritis partially or fully closed the lumen of the various arteries." Some of these changes are similar to those described in the placenta with lupus erythematosus. Figure 2 is from the original publication.

DeBeukelaer et al.[14] in 1973 reported a patient with polyarteritis nodosa in whom corticosteroids induced a remission. Four years later she conceived, and her pregnancy was relatively uneventful. Following labor at 34 weeks, she delivered a 2.2-kg female, and both the mother and the infant did well. Noting that previous patients had died postpartum, these authors treated her with high doses of corticosteroids and sex steroid hormones beginning with delivery.

The case reported by Reed and Smith[15] in 1980 was that of acute onset of hypertension

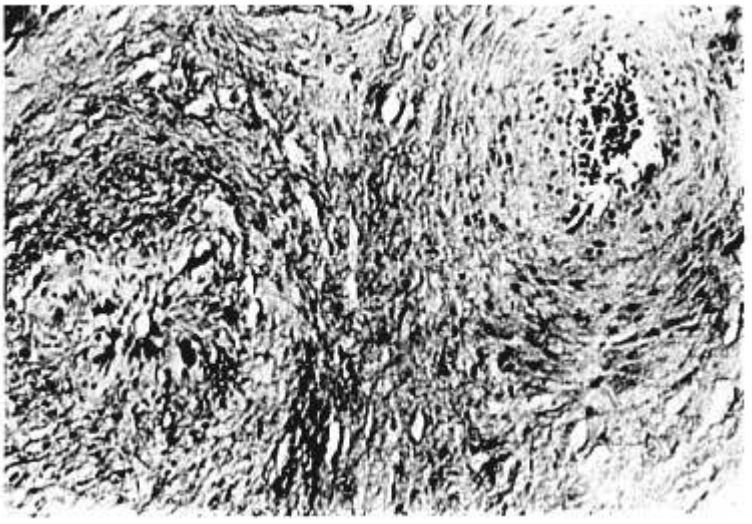

FIG. 2. *Photomicrograph of placenta in case of polyarteritis nodosa demonstrating obliterative endarteritis. (From Szinnyai et al.[13] By permission.)*

and other systemic symptoms in the first trimester, leading to a clinical diagnosis of polyarteritis nodosa. Spontaneous abortion and a progressive downhill course with death in uremia occurred in spite of high-dose prednisone therapy. The most recently reported case, that of Barkett and Richards[16] in 1982, involved a patient who conceived 2 years after the disease was diagnosed. She was on prednisone and in remission, although there was evidence of renal disease. Pregnancy was complicated by progressive hypertension, which prompted induction of labor at 37 weeks. A healthy 3.15-kg male infant was delivered. The woman did well until 18 months postpartum, when she experienced exacerbation of her disease and died in renal and cardiac failure.

In 7 of the 10 reported cases of pregnancy complicated by polyarteritis nodosa, the disease had its onset, at least clinically, during pregnancy or in the immediate postpartum period, and in all 7 maternal death resulted. Two of the 7 occurred in early gestation and resulted in abortion; the other 5 women all produced liveborn infants. The 3 patients in whom the disease had been diagnosed prior to pregnancy and was in remission all did reasonably well. Something resembling superimposed preeclampsia developed in 2 of the 3 and was associated with fetal death in 1, but all 3 mothers survived. Thus, it appears that patients whose disease is such that they survive long enough to conceive have a reasonable outlook for the gestation, albeit with some increased risk. Acute onset and severe manifestations during pregnancy, on the other hand, carry an ominous prognosis.

Not included in this review are cases in which the involvement was entirely cutaneous for, as summarized previously, it is difficult to determine whether this represents a different disease or another stage of the same disease. In this regard, however, a case reported by Boren and colleagues[17] is of particular interest in that it described a woman with cutaneous vasculitis whose newborn infant developed similar lesions shortly after birth. Another case of interest is that of sudden and unexpected death of a previously healthy gravida near term in which the autopsy reviewed isolated coronary periarteritis and thrombosis.[18]

Diagnosis and Treatment

With all rare conditions, the key to diagnosis is to think of the disease. In the case of polyarteritis nodosa, a number of the clinical features (Table 1) are those of much more common obstetric complications, particularly pregnancy-induced hypertension. Thus, it is not surprising that most of the reported cases (Table 3) were diagnosed as some type of pregnancy-associated hypertensive condition. The presence of fever and other manifestations of multi-system disease and the apparent early-onset or otherwise atypical preeclampsia should suggest the possibility of polyarteritis nodosa. Careful physical examination is essential, because although subcutaneous nodules are found in only a minority of cases, their presence can be a crucial observation in making the diagnosis.

Initial treatment should consist of corticosteroids, typically prednisone, in daily doses of 40–60 mg initially. If a response follows, as it does in some instances, the dose should be tapered to the lowest level compatible with control of symptoms and signs. In nonresponders, early consideration should be given to immunosuppressive or cytotoxic agents. Certain concerns, summarized in another chapter in this symposium, have been raised about these drugs in pregnancy. However, the suggestions of their efficacy in treating this disease, coupled with the poor prognosis in untreated cases, argues for an aggressive approach. The suggested regimen is that of Fauci et al., i.e., cyclophosphamide in a dose of 2 mg/kg/day orally. Corticosteroids should be tapered toward an alternate-day schedule with the aim of ultimate discontinuation.

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