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Cutaneous polyarteritis nodosa

'Cutaneous polyarteritis nodosa' is a term which may refer to cutaneous manifestations of systemic polyarteritis nodosa (PAN) as well as a benign cutaneous PAN, which represents a more limited form (15).

Cutaneous polyarteritis nodosa (CPN, c-PAN), first described by Lindberg in 1931, is a chronic, relapsing, benign course characterized by the absence of systemic involvement. For a long time the existence of CPN as a distinct entity was a matter to debate, because it was believed to represent an early stage of PAN. However, recent studies with a long-term follow-up have clearly shown that CPN rarely progress into PAN (13). Polyarteritis nodosa is a systemic disease classified as a vascular collagenosis. The disease was first described by Kussmaul and Maier in 1866. On the basis of the localization and the macroscopic image they introduced the term of *'periarteritis nodosa'*. For many years it became common for most of the systemic forms of vasculitis. At the beginning of 1900 Ferrari and Dickson introduced the notion of *'polyarteritis nodosa'* in order to emphasize the polyarterial character of the process as well as the localization of changes not only around arteries but also in every layer of the vascular walls. In 1948 Davson and his associates suggested the division of PAN into two groups depending on the presence of or the lack of glomerulonephritis. It allowed for the separation of the microscopic polyangiitis (mPA) and the classic form (cPA).

mPA mainly applies to small vessels (arterioles, venules, capillary vessels) and is one of the most frequent causes of necrotizing glomerulonephritis. The serologic marker is autoantibodies against neutrophilic granulocytes and monocytes – ANCA (c-ANCA react with serine proteinase -3, in the intermediary immunofluorescence they produce scattered light in cytoplasm and p-ANCA – antibodies with perinuclear light, reacting with myeloperoxidase).

The classic form of PAN (cPA), defined at the Chapel Hill Conference in 1994, is a medium and weak necrotizing arteritis, which does not affect the smallest vessels and is not the cause of glomerulonephritis (11).

Polyarteritis nodosa occurs in all the ethnic groups with the frequency of 6–7 cases per 100,000 people in a year. It may reveal itself at any age, also in newborns. Vasculitis in a newborn to a mother who has vasculitis is a rare event. A literature review produced only isolated cases (12). However, the first symptoms occur between 35 and 55 years of age most often. Men become ill three times as often. The systemic form is less favourable in children than in adults, the prognosis of cutaneous PAN is the same in childhood as it is in adults (1). The nature of PAN is the occurrence of infiltrative, necrotic and inflammatory changes. They spread over the small and medium muscle arteries, mostly in the place of bifurcations. Macroscopically, they are characterized by nodular thickenings occurring along the vessel routes, forming the image similar to the string of pearls (8). Microscopically, segmental thickening of all the vascular layers is confirmed. In the area of middle coat, where the inflammatory process begins, fibrinoid necrosis, pleomorphic inflammatory

infiltrations from lymphocytes (especially CD4+), macrophages and granulocytes are visible. In some patients there occur immunologic complexes consisting of HBs antigen, anti-HBs antibodies, IgG, IgM immunoglobulins and C3 fraction of the complement (11).

In the course of the disease, due to the damage of vascular walls and the production of fibrous tissue, the proceeding stenosis or complete obliteration of vessels occur. It is connected with the occurrence of thrombuses, areas of infarction or hemorrhage, which lead to ischemia of the supplied tissues. The changes may be the cause of death if they are localized in life-important organs (8).

The cause of PAN is not fully known. In the pathomechanism, the deposition of immunological complexes in the vascular walls is likely to have an essential effect. Among the causal factors, viral infections play a huge role, especially infections of hepatitis virus type B. In 30–70% of patients, permanent or temporary antigenemia HBs is confirmed. Presently, owing to common availability of the vaccine against WZW B, the number of new cases connected with HBV is estimated at less than 10% (11). The presence of antigen HBs is connected with the acute course of PAN and higher mortality in the first year of the disease. Vasculitis normally develops after about three-four months from the clinical hepatitis, whereas the degree of expansion and the advancement of hepatic lesions is often incommensurately mild compared with the intensification of vascular lesions (11). The causes of the disease might also be: parvovirus B19, streptococci of the group A, hepatitis virus C, cytomegalovirus and HIV virus. Among other causes there are hypersensitivity reactions to various chemical substances such as: arsenic, iodine, sulphonamides, barbiturates, thyouracil and some antibiotics (7). The familial occurrences of the disease, the coexistence with hairy cell leukemia and a case of polyarteritis nodosa as the first manifestation of gastric carcinoma have also been reported (7, 11). In spite of numerous examinations, in 2/3 of the patients ill with polyarteritis nodosa it is impossible to determine the causes of the disease (12).

Polyarteritis nodosa is characterized by a rich and varied clinical image. The disease may affect every organ, have a limited form or have a systemic character. Most frequently the lesions are found in the vessels of the skin, the nervous system, the kidneys, the myoskeletal system, the cardiovascular system and the alimentary tract.

In CPN lesions are limited to skin, adjacent muscles, nerves and joints. There is no systemic involvement observed. The characteristic pathologic feature is a leucocytoclastic vasculitis in the small- to medium-sized arterioles of the deep dermis or hypodermis, with or without associated fibrinoid necrosis. The histopathological findings can be divided into four stages: 1) degenerative stage with degeneration of arterial wall and deposition of fibrinoid material and partial or complete destruction of internal and external elastic laminae, 2) acute inflammatory stage with an infiltrate mostly composed of neutrophils with some eosinophils around and within the arterial wall, 3) granulation tissue stage with an infiltrate also containing lymphocytes and macrophages and intimal proliferation and thrombosis with occlusion of the lumen leading to ulceration, 4) healed end-stage with fibroblastic proliferation extending in the perivascular area. Immunoglobulin M or C3 deposition in the vessel walls has been found occasionally (1, 15).

The precise etiology of c-PAN remains unknown. Contrary to systemic PAN, there is no evidence to indicate that immunological mechanisms have any role in the pathogenesis of cutaneous polyarteritis nodosa. Several infectious and noninfectious conditions have been associated both with initiation and relapse of the disease. Among them, streptococcal infection has been commonly implicated. Beside *Streptococcus*, other infectious agents, such as *Parvovirus* B19 and *Mycobacterium* have been implicated in the pathogenesis of c-PAN. Hepatitis viruses B and C have been implicated mainly in the pathogenesis of systemic PAN, and they have been associated with cutaneous PAN only in isolated cases (4,14). c-PAN can also be associated with connective tissue diseases (*lupus erythematosus*,

rheumatoid arthritis), Wegener's granulomatosis, Churg-Strauss syndrome, myasthenia gravis, and other settings. Azathioprine may induce vasculitis, which is generally observed 8–15 days after beginning the treatment (3, 5, 6).

Skin lesions may be preceded by systemic symptoms. They are atypical, shared by many diseases. Most frequent symptoms are fever, malaise, myalgia, arthralgias, arthritis (knees, elbows) and neuropathy. The joint lesions are migrating, temporary, usually non-deforming and non-destructive. They apply to about 50% of patients. In the case of seronegative arthritis, moderate leucocythosis with neutrophilic granulocytes prevailing is reported to appear in the intra-articular fluid. Acrocyanosis and Raynaud's phenomenon were seen in isolated cases. Peripheral neuropathy manifested as numbness, burning sensation and paraesthesias has been reported in about 20% of patients. The neurological complaints seem to be more common in severe cases of cutaneous PAN (4, 9). Several cases with the acral necrosis of the fingers as initial manifestation of c-PAN have been described (13, 15).

The lower extremities are the most common skin lesions' localization, however, upper extremities and the trunk may also be affected. c-PAN is a chronic relapsing disorder. The clinical manifestations are characterized by the presence of subcutaneous tender, erythematous nodules 0,5-3 cm in diameter. They may disappear spontaneously or undergo ulceration. Painful ulcers, which are caused by severe local vascular inflammation, occur in 50% of patients. Whether ulceration changes the prognosis of the illness is not known. The skin lesions also include livedo reticularis, purpura, extravasations, oedema and swelling of the lower extremities (4, 6, 13).

The diagnosis is made by clinical and laboratory findings. The laboratory values are often not impressive in c-PAN. Increased erythrocyte sedimentation rate is found in 60–94% of patients and mild anaemia in one-third of patients. Findings like persistent proteinuria, high blood pressure, the presence of leucocytosis and eosinophilia, which are characteristic in systemic PAN and giving rinse to a poor-term prognosis, are not observed in c-PAN (1). Immunological testing does not appear helpful in confirming the diagnosis of cutaneous PAN, however, negative results for these tests help to exclude other systemic vasculities. Cutaneous polyarteritis nodosa is confirmed by the histopathological findings. A deep incisional biopsy, including subcutaneous tissue, is necessary for the accurate diagnosis of the disease (4).

Cutaneous PAN does not require the intense treatment to bring about remission that is necessary for systemic PAN. Most patients can be kept in remission with low-dose corticosteroid therapy (prednisone at a daily dose of 20–60 mg). Mild cases can be treated with non-steroidal anti-inflammatory agents alone or in combination with a low dose of prednisone (20 mg/day). A long course of treatment with antibiotics may be needed in patients with documented streptococcal or other bacterial infections. If there is no response, low doses of methotrexate have been used with good responses (4, 6, 13).

In summary, cutaneous polyarteritis nodosa is a distinct clinical entity characterized by a chronic, relapsing, benign course and the absence of systemic involvement. Because cutaneous involvement may occur in 20–40% of cases of systemic PAN and systemic disease has developed in a few patients after a variable period of follow-up, from 1 to 20 years, it is very important to check patients with CPN carefully to exclude systemic, often life-threatening involvement (1, 2, 4, 10).

REFERENCES

1. Bauza A. et al.: Cutaneous polyarteritis nodosa. Br. J. Dermatol., 146, 694, 2002.
2. Bravi P., Martini P.: Polyarteritis nodosa cutanea: a case report. Reumatismo, 55, 108, 2003.
3. Chen H-H. et al.: Successive development of cutaneos polyarteritis nodosa, leucocytoclastic vasculitis and Sweet's syndrome in a patient with cervical lymphadenitis caused by *Mycobacterium fortuitum*. Br. J. Dermatol., 151, 1096, 2004.
4. Daoud M. S. et al.: Cutaneous periarteritis nodosa: a clinicopathological study of 79 cases. Br. J. Dermatol., 136, 706, 1997.
5. Durst R. et al.: *Parvovirus* B19 infection associated with myelosuppression and cutaneous polyarteritis nodosa. Rheumatology, 41, 1210, 2002.
6. El Sayed F. et al.: Myasthenia gravis with cutaneous polyarteritis nodosa. Clin. Exper. Dermatol., 31, 215, 2006.
7. Henderson J. et al.: Polyarteritis nodosa presenting as a pyrexia of unknown origin. Postgrad. Med. J., 78, 685, 2002.
8. Kotulska A., Kucharz E. J.: Guzkowe zapalenie tętnic. Pol. Arch. Med. Wewn., 104, 507, 2000.
9. Mimouni D. et al.: Cutaneous polyarteritis nodosa in patients presenting with atrophie blanche. Br. J. Dermatol., 148, 789, 2003.
10. Orton D. I., Whittaker S. J.: Renal angiogram abnormalities in a case of cutaneous polyarteritis nodosa. Clin. Exp. Dermatol., 25, 33, 2000.
11. Stone J. H.: Polyarteritis nodosa. JAMA, 288, 1632, 2002.
12. Stone M. S. et al.: Cutaneous vasculitis in the newborn of a mother with cutaneous polyarteritis nodosa. J. Am. Acad. Dermatol. 1993, 28, 101, 1993.
13. Stussi G. et al.: Acral necrosis of the fingers as initial manifestation of cutaneous polyarteritis nodosa. A case report. Angiology, 52, 63, 2001.
14. Tang M. B. Y. et al.: Cutaneous polyarteritis nodosa associated with precore mutant hepatitis B infection. Br. J. Dermatol., 149, 914, 2003.
15. Won Choi S. et al.: Cutaneous polyarteritis nodosa presented with digital gangrene: a case report. J. Korean Med. Sci., 21, 371, 2006.

SUMMARY

'Cutaneous polyarteritis nodosa' is a term which may refer to cutaneous manifestations of systemic polyarteritis nodosa (PAN) as well as a benign cutaneous PAN (CPN, c-PAN), which represents a more limited form. CPN, in contrast to PAN, is a benign, limited to skin, adjacent muscles, nerves and joints, with a good prognosis disease. There is no systemic involvement observed. Because cutaneous involvement may occur in 20–40% of cases of systemic PAN and systemic disease has developed in a few patients after a variable period of follow-up, from 1 to 20 years, it is very important to check patients with CPN carefully to exclude systemic, often life-threatening involvement.

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'Cutaneous polyarteritis nodosa' jest terminem używanym dla określenia zmian skórnych w uogólnionej postaci guzkowego zapalenia tętnic (*polyarteritis nodosa*, PAN), jak również odnosi się do skórnej postaci guzkowego zapalenia tętnic (*cutaneous polyarteritis nodosa*, CPN, c-PAN). CPN w przeciwieństwie do PAN jest łagodną, ograniczoną do skóry, przyległych mięśni, nerwów i stawów, dobrze rokującą chorobą. Nie obserwuje się zajęcia narządów wewnętrznych. Biorąc jednak pod uwagę fakt, że charakterystyczne dla CPN zmiany skórne występują w 20–40% przypadków uogólnionej postaci PAN, jak również uwzględniając pojedyncze opisy przypadków, w których w ciągu 20 lat od wystąpienia objawów skórnych rozwinęła się uogólniona postać PAN, niezwykle istotną rolę odgrywa systematyczne monitorowanie stanu ogólnego pacjenta w celu wykluczenia wielonarządowych, często zagrażających życiu zmian.