ISOLATED CUTANEOUS VASCULITIS ASSOCIATED WITH POLYNEUROPATHY

Polinöropati ile birlikte seyreden izole cilt vasküliti

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Abstract: *A 26 year-old- woman with neuropathy developed erythema, purpura, bullous lesions and subsequent ulcers on the anterior aspects of right leg and left ankle. Pathological examination of punch biopsy specimens taken from ulcerative lesions manifested leukocytoclastic vasculitis. Peroneal nerve and fibular brevis muscle biopsies revealed axonal neuropathy without vasculopathy. The cutaneous vasculitis may be associated with systemic disease or rarely may lead to peripheric polyneuropathy. In cutaneous vasculitis exogenous (i.e.drugs, infectious agents) or endogenous (i.e.malignancies, connective tissue diseases) etiologies have been accused. In the current study we report a very typical patient with isolated cutaneous vasculitis associated with polyneuropathy presumably due to streptomycine injection.*

Key Words: *Polyneuritis, Vasculitis*

Özet: *Yirmialtı yaşında nöropatili bayan hastanın sağ ayak ön yüzünde ve sol ayak bileğinin arka yüzünde eritem, purpura ve büllöz karakterli olup sonradan ülserleşen lezyonlar gelişti. Ülsere lezyonlardan alınan biyopsi materyalinin patolojik inceleme sonucu lökositoklastik vaskülit olarak bildirildi. Peroneal sinir ve fibuler brevis kas biyopsilerinde aksonal nöropati gözlendi fakat vaskülit mevcut değildi. Cilt vaskülitleri sistemik hastalıklarla birlikte olabileceği gibi nadir de olsa periferik polinöropatiye yol açabilir. Cilt vaskülitlerinde ekzojen (ilaç kullanımı, enfeksiyöz ajanlar gibi) ya da endojen (maligniteler, bağ dokusu hastalıkları) etyolojiler araştırılmalıdır. Bu çalışmada streptomisin enjeksiyonuna bağlı olabileceği düşünülen izole cilt vasküliti ve polinöropati birlikteliği rapor edildi.*

Anahtar Kelimeler: *Polinöropati, Vaskülit*

Polyneuropathy may occur at any age and the clinical manifestations depend on the severity and distribution of the lesions as well as the extent of functional deficiencies and etiologic factors. In the diagnostic evaluation of polyneuropathy a detailed familial, social and medical history, neurological examination, electrodiagnostic, biochemical and microscopic investigations must be performed although the efforts can sometimes be fruitless. Hypersensitivity vasculitis (systemic or cutaneous) should be suspected in any patient with progressive dysesthetic polyneuropathy.The symptoms of cutaneous vasculitis such as urticarial erythema, palpable purpura, papulae, bullae, nodules and ulcerations vary depending on the size of the affected blood vessel, degree and natural course of inflammation (1). The most common causes of vasculitic neuropathy are polyarteritis nodosa (PAN) and hypersensetivity angiitis. Clinically, it may be difficult to distinguish between PAN, the overlap syndrome and systemic hypersensitivity angiitis. A diagnosis of cutaneous vasculitis (PAN or Leukocytoclastic vasculitis) should be considered in any patient with neuropathy. The diagnosis can usually be confirmed by biopsy of full thickness dermis and epidermis from a recent skin lesion.

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CASE REPORT

A 26 -year-old Turkish woman had a one month history of progressive difficulty in walking. She was unable to walk independently and sometimes had complaints of arthralgia, abdominal pains. There were painful burnings, paresthesias and sensory loss of all types in extremities. There was a history of four months' pregnancy. One and a half month ago she visited an orthopedist and a neurologist because of unbearable low back pains. The neurological examination was normal and she was diagnosed as having sacroileitis and streptomycin was prescribed for 10 days. Subsequently muscular weakness and severe calf pains developed making her unable to walk or stand. Neurologic examination revealed sensory deficit in all extremities predominantly in a "stocking and glove" distribution. There was a complete loss of deep sensations. There was no pyramidal signs. Hand muscles innervated by the ulnar nerve were atrophic. Distal weakness was more prominent in the ankle and big toes during dorsiflexion. Except for the diminished right triceps jerk, deep tendon reflexes were absent on both sides. Both plantar reflexes were refractory to stimulation. Magnetic resonance imaging of spinal cord was found to be normal. Electroneuromyography (ENMG) provided evidence of mixed type polyneuropathy more evident in lower extremities (Table I).

EEG was normal. CSF findings were normal with the exception of high protein levels. A diagnosis of polyneuropathy was made and supportive treatment was initiated. Pharmacotherapy with carbamezapine, anticholinergics, vitamine B2 and B6 complexes were administered and a rehabilitative exercise program was followed. Erythrocyte sedimentation rate was 35 mm/hour. Serum T4 exceeded 17.05 ng/dl (N: 4.5-12 ng/dl). Abnormal serum TSH 0.256 mIU/ml (N: 0.49-4.67 ng/dl), free T4 3.11 ng/dl (N: 0.71-1.85 ng/dl) and IgM 4.14 g/l (N: 0.7-2.8 g/l) values were detected Anti-cardiolipin IgG and IgM values were elevated (10.8 GPL U/ml and 21.6 MPL U/ml; N: <7.2 U/ml and <6.5 U/ml respectively). All the relevant serum biochemical tests including serum complements, cryoglobulins, HIV, HBs and lyme antibodies, immune globulins, autoantibodies, ANCA, B12 were found to be normal. Scintigraphy revealed a toxic nodular goitre. Electrocardiographic and abdominal ultrasonographic findings suggested no abnormality. After two weeks of streptomycine administration, erythema, purpura, bullous lesions and then ulcerations had become apparent on the anterior aspects of the right leg and the left ankle. A punch biopsy revealed leucocytoclastic vasculitis. Peroneal nerve and fibular brevis muscle biopsies demonstrated axonal degeneration and denervations without vasculitis. Corticotherapy (prednisone 60 mg/day) was initiated. Treatment produced prominent and partial improvement in cutaneous lesions and neurological findings respectively. She could walk alone and perform her routine daily activities by herself. At the end of 2 months of treatment, there was no marked alteration in the ENMG.

Table I. ENMG findings

ENMG no:	Nerve	Conduction velocity (m/sec)	Distal latency m sec	SNAP (μV) CMAP (mV)	F response
Motor	Right peroneal				
	Pop.fossa - Cap.fibula	30.4	16.2		-
FIRST ENMG	Cap.fibula – Ankle	35.5	13.4	1.84	-
	Ankle - Ext.digitor.brevis		5.8	2.74	-
	Right posterior tibial			3.13	
	Pop.fossa - Med.malleolus				
	Med.malleolus - Flex.hall.brevis	36.5	16.4		-
	Right median		6.0	2.47	-
	Elbow -Wrist			4.19	
	Wrist - Abd.poll.brevis	56.9	6.86		
	Right ulnar		3.08	4.3	28.7
	Upper arm - lower arm			5.5	
	Lower arm - wrist				
	Wrist - Abd.dig.minimi	51.02	8.12		
		54.23	6.16	12.05	
			2.38	11.96	29.54
				12.74	
Motor	Right peronal				
	Pop.fossa - Cap.fibula				
SECOND ENMG*	Cap.fibula – Anklet	35.7	14.0	5.0	
	Ankle - Ext.digitor.brevis	34.7	11.2	5.0	
	Right posterior tibial		4.0	7.0	
	Pop.fossa - Med.malleolus				
	Med.malleolus - Flex.hall.brevis	36.97	13.6	7.0	
	Right median		4.0	10.0	56.8
	Elbow - Wrist				
	Wrist - Abd.poll.brevis				
	Right ulnar	48.9	7.6	9.0	
	Above elbow – below elbow Below		3.2	10.0	
	elbow - Wrist				
	Wrist - Abd.dig.min.	52.5	7.6	5.0	
		51.4	5.6	7.0	
			2.0	9.0	27.6
Sensorial	Right sural	No response was			
	(Lat.Mall.- Mid-calf)	obtained			
FIRST ENMG	Right median				
	(Wrist – 3rd digit)	No response was			
	Right ulnar	obtained			
	(Wrist – 5th digit)		5.08		
		26.0		7.0	
Sensorial	Right sural	No response was			
		obtained			
SECOND ENMG*	Right median				
		No response was			
	Right ulnar	obtained			
		24.1	5.6	13.5	

**The second ENMG : following 2 months of prednisone treatment and supportive management. Muscle-motor unit action potential was found to be normal.*

***CMAP**: Compound Muscle Action Potential. **SNAP**: Sensorial Nerve Action Potential.*

DISCUSSION

Neurological signs and symptoms are usually not observed unless the adjacent cutaneous nerves are unusually involved in the inflammatory process. Neurological manifestations occur in 5% of cutaneous vasculitis and are limited to polyneuropathy (2). Leukocytoclastic vasculitis must be suspected in any patient with progressive dysesthetic polyneuropathy. Drug induced leukocytoclastic vasculitis is a late cytotoxic reaction which typically becomes evident after 3- 6 days of drug administration. However this reaction may be delayed as long as 21 days with slowly metabolised drug. The presence of skin lesions, eosinophilia, unexplained fever or any combination of these should lead to a suspicion of a drug induced vasculitis. Occasionally a drug which has been well tolerated for years may suddenly cause vasculitis (3).

Erythema, purpura and leg ulcers are recognised manifestations of drug induced cutaneous vasculitis (4). Vesicles, hemorrhagic bullae and necrotic lesions appear in the short run and subside within two or three weeks. Purpurae most often appear on the lower extremities and on dependent areas of the body or regions under local pressure. The spectrum of manifestations varies widely from erythema to urticariae (5). Cutaneous hypersensitivity vasculitis is generally benign in nature and may be less commonly characterised by albuminuria, urinary sediment abnormalities, abdominal pain and pulmonary signs and symptoms in contrast to PAN. In addition an idiopathic form has been described. In one third of the patients non-deforming arthritis and arthralgia have been detected (6).

In patients with all forms of leukocytoclastic vasculitis, an elevated erythrocyte sedimentation rate is the most frequent abnormal laboratory finding. In the cutaneous form, serum complement system is usually normal.

The presence of IgM was detected with an increasing frequency in patients with arthritis and systemic or cutaneous necrotising vasculitis (7). There is not any correlation between circulating anti-cardiolipin antibodies and the incidence of systemic vasculitis of interstitial neurological characteristics but they may serve as an additional marker indicating a potential risk of cutaneous vasculitis (8).

Our therapeutic approach is based on clinicopathological findings. The most commonly encountered pathology is an acute necrotising process with a predominantly eosinophilic infiltration of all three vascular layers stuffed with nuclear debris .The lesions show the same stage of evolution. The skin lesions are pathognomonic and provide an access to the understanding of pathologic process. If there is still a doubt about the etiologic diagnosis after the completion of electrodiagnostic tests nerve biopsy must be performed.

Although the treatment with colchicine, dapsone, corticosteroids and immunosuppresive agents has been reported as beneficial in isolated cases, controlled clinical trials are not yet conclusive (9). Steroids exert a highly variable effect. Most patients require only warmth and rest. Antihistamines of H1 type may be used to alleviate cutaneous symptoms. Ulcers are generally managed by local measures.

In our patient, polyneuropathy developed within one week after the administration of streptomycine. The clinical picture and histopathology suggest the possible drug mediated vascular impact. Any relevant abnormal laboratory finding must be considered as an indication of potential cutaneous vasculitis.

There is a recently described distal accentuation of conduction slowing in association with IgM monoclonal gammopathy and antibodies to myelin associated protein (10). Our patient also had elevated spinal fluid protein. IgM gammopathies are characterised by organomegaly and lymphadenopathy. It is seen in older ages. Hyperviscosity problems, anemia, retinal hemorrhages can be seen. In our patient there was no hematological abnormalities likely to be seen in

gammopathies. The electrodiagnostic studies of our patient indicate only borderline slowing of conduction velocities but normal distal latencies of all motor nerves and no demyelination. Accordingly, a more likely diagnosis to entertain is a cutaneous hypersensitivity vasculitis mediated neuropathy as opposed to an immune mediated neuropathy. Clinically, it is difficult to distinguish between PAN, overlap syndrome and systemic hypersensitivity vasculitis. The neurologic manifestations are of cardinal importance for PAN because they tend to be the least reversible and are associated with very high morbidity. Mononeuritis multiplex (MNM) is probably the most significant clinical sign of PAN. Many investigators have reported concurrence of MNM and polyneuropathy. Wees and associates found evidence of vasculitis in sural nerve biopsies in 100% of 15 patients with abnormal sural nerve conduction velocity or amplitude in systemic vasculitis (11). Gastrointestinal tract and cardiac involvements may be present in PAN or overlap syndromes. With ocular involvement, hypertensive changes are most common, followed by ocular vasculitis and optic disc edema or atrophy in classic PAN. Isolated cutaneous form of PAN is present and natural history of this disorder is that of a chronic course with a good long-term prognosis. Our patient had a history of progressive symptoms and subacute clinics. An underlying collagen vascular disesase or a history of drug treatment is present in one third of cutaneous hypersensitivity vasculitis patients.

Neurologic manifestations occur in only 5% of patients and are limited to polyneuropathy in cutaneous hypersensitivity form. There was no history of collagen vascular disease but drug treatment in our patient. Hypersensitivity vasculitis secondary to streptomycin was cited in the literature (12), but we have not encountered any report of cutaneous vasculitis induced polyneuropathy secondary to streptomycine administration.

Since there was a long time before the onset of polyneuropathy and skin lesions, pregnancy was not considered to be a facilitative factor in the development of vasculopathy. Corticosteroid administration and supportive management has caused marked and partial improvement in our patient's cutaneous lesions and neurological findings respectively at the end of two months of treatment. Favorable responses to steroids have been reported in isolated cutaneous hypersensitivity vasculitis.

It would be unusual to manifest such a severe neuropathy before any cutaneous lesions and without a significantly elevated ESR. Our patient described itching and some erytematous lesions within last two months but the main lesions (palpable purpura, ulcers) were seen after neuropathy.

In conclusion, with respect to clinical and etiological point of view, this patient represents a rare case of isolated cutaneous vasculitis induced polyneuropathy presumably due to streptomycin injection therapy.

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