นิพนธ์ต้นฉบับ

Paraneoplastic syndrome of the nervous system.

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Paraneoplastic syndromes of the nervous system (PNPS) are disorders of unknown cause that occur in patients with occult or identifiable malignancy. Their manifestations are protean. Data concerning 20 patients with PNPS are presented. The most common PNPS were syndromes involving the peripheral nervous system and muscle, these included 6 cases of peripheral neuropathy, 3 cases of myasthenia gravis, 1 case of myasthenic syndrome, 1 case of myopathy and 2 cases of polymyositis. The central nervous system manifestations were: 1 case of encephalopathy, 2 cases of dementia, 1 case of cerebellar atrophy, 1 case of opsoclonus, 1 case of subacute combined degeneration of the spinal cord, and 1 case of amyotrophic lateral sclerosis. The most common pathological finding in this series was central and peripheral demyelination. The underlying malignancies were: 4 cases of breast cancer, 2 cases each of lung cancer, leukemia, plasmacytoma, nasopharyngeal carcinoma, malignant thymoma and metastatic tumor and 1 case each of lymphoma, bladder carcinoma, mutiple myeloma and hepatocellular carcinoma. The most common abnormality in routine investigation was an elevated CSF protein. The clinical course, response to therapy of these cases, the pathogenesis as well as clinical investigation of this entity are discussed.

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กลุ่มอาการพารานีโอพลาสติกของระบบประสาท เป็นกลุ่มอาการที่ยังไม่ทราบสาเหตุแน่นอน กลุ่มอาการนี้จะพบในผู้ป่วยที่เป็นมะเร็งทั้งชนิดที่เป็นแบบซ่อนเร้น และในผู้ป่วยที่ได้รับการวินิจฉัยว่าเป็นมะเร็งอยู่แล้ว อาการของผู้ป่วยในกลุ่มนี้มีได้มากมายหลายอย่าง คณะผู้วิจัยได้ทำการวิเคราะห์ข้อมูลของผู้ป่วยที่มีอาการนี้จำนวน 20 ราย กลุ่มอาการที่พบบ่อยที่สุดคือ กลุ่มอาการที่เกิดกับระบบประสาทส่วนปลายและกล้ามเนื้อ ซึ่งพบว่ามีโรคของเส้นประสาทจำนวน 6 ราย, โรคไมแอสทีเนียกราฟวีสจำนวน 3 ราย กลุ่มอาการไมแอสทีนิกจำนวน 1 ราย โรคกล้ามเนื้อจำนวน 1 ราย และโรคกล้ามเนื้ออักเสบจำนวน 2 ราย กลุ่มอาการที่เกิดกับระบบประสาทส่วนกลางพบว่าเป็นเอ็นเซ็บพาโลพาที 1 ราย กลุ่มอาการสมองเสื่อม 2 ราย โรคสมองน้อยฝ่อ 1 ราย ออพโซโคลนัส 1 ราย และอาการเสื่อมของไขสันหลัง 2 ราย พยาธิสภาพที่พบบ่อยที่สุดคือ การเสื่อมสลายของไมอีลินทั้งในระบบประสาทกลางและระบบประสาทส่วนปลาย มะเร็งที่เป็นสาเหตุของกลุ่มอาการนี้พบมะเร็งเต้านม 4 ราย, มะเร็งปอด, มะเร็งของเม็ดโลหิตขาว, พลาสมาไซโตมา, มะเร็งของโพรงจมูก, มะเร็งของต่อมไทมัส, มะเร็งแพร่กระจายอย่างละ 2 ราย ลิมโฟมา, มะเร็งของกระเพาะปัสสาวะ, มัลติเพิลไมอีโลมา, และมะเร็งตับ อย่างละ 1 ราย การตรวจทางห้องปฏิบัติการที่ผิดปกติที่พบบ่อยคือ การมีโปรตีนในน้ำไขสันหลังเพิ่ม นอกจากนี้ยังได้วิเคราะห์การดำเนินโรค การตอบสนองต่อการรักษา และได้เสนอแนะเกี่ยวกับพยาธิกำเนิดและแนวทางการตรวจหามะเร็งในผู้ป่วยที่มาด้วยกลุ่มอาการเหล่านี้

Paraneoplastic syndromes of the nervous system (PNPS) are clinical neurologic syndromes occuring in cancer patients for which metastasis, invasion, compression, metabolic disorder, complications from therapy, hemorrhage or infection cannot be causally implicated[1,2]. PNPS are protean in their manifestations and these syndromes are either clearly paraneoplastic or strongly associated with cancer. In general PNPS are rare[3], but they are likely to be discovered more frequently as patients with cancer live longer and are exposed for longer periods to what are often literally malignant influences. The clinical importance of PNPS does not lie in the number of patients affected. Instead, the syndromes may be helpful in discovering a hidden malignant lesion, or monitoring response to cancer therapy. Elimination of cancer can reverse the patient's dominant symptoms and thus provide significant clinical palliation.

MATERIALS AND METHODS

Twenty patients presented with PNPS defined as central, peripheral or combined lesions of the nervous system in the duration of ten years were studied. In these patients the evidence of nervous system involvement was confirmed by medical history, neurological examination plus autopsy, biopsy. or electrodiagnostic or other appropriate tests. Metastasis, invasion, compression, metabolic disorder, hemorrhage, infection or complications from therapy which might have caused the syndromes were excluded by history, physical examination, appropriate biochemical, serological and radiological investigations. CT-scan of the brain was performed in all cases with central nervous system involvement, and a myelogram was performed in all cases with suspected spinal lesions. Cerebrospinal fluid (CFS) analysis with cytologic examination was done in all cases except in those of myopathy or neuromuscular junction diseases. All types of associated malignancies were confirmed histologically, with the exception of Case 4 whose diagnosis was made on the basis of classical radiologic feature of pulmonary malignancy and a high carcin-oembryonic antigen level.

RESULTS

The age and sex distribution of the patients, type of PNPS, site of associated malignancy, and histologic type of malignancy are shown in Table 1.

Table 1 Age, Sex, PNPS, primary site of cancer and histologic type of cancer in paraneoplastic syndromes of the nervous system.

Case	Age	Sex	PNPS	Primary site of Cancer	Histologic type of Cancer
1	41	M	Encephalo-Radiculopathy	Liver	Hepatocellular carcinoma
2	66	F	Dementia with Psychosis and Neurogenic bladder	Breast	Poorly differentiated ductal cell carcinoma
3	36	F	Dementia with Parkinsonism	Breast	Adenocarcinoma
4	92	F	Opsoclonus	Lung	Carcinoma?
5	72	M	Cerebellar atrophy	Lung	Bronchio-alveolar carcinoma
6	54	M	Subacute combined degeneration of spinal cord	Systemic	Acute monoblastic leukemia
7	45	F	Amyotrophic lateral sclerosis involving spinal cord and brainstem	Breast	Infiltrating ductal carcinoma
8	18	M	Gllilain-Barŕe syndrome with optic neuropathy	Systemic	Acute myelomonoblastic leukemia
9	59	M	Motor neuropathy	Bone, ilium	Plasmacytoma (osteosclerotic type)
10	30	M	Motor neuropathy with bilateral papilledema	Spine	Plasmocytoma(osteolytic & osteosclerotic type)
11	71	M	Sensorimotor neuropathy	Metastatic carcinoma bone	Adenocarcinoma

Table 1 (Cont'd)

Case	Age	Sex	PNPS	Primary site of Cancer	Histologic type of Cancer
12	51	M	Sensorimotor neuropathy	Nasopharynx	Non-keratinizing squamous cell carcinoma
13	57	F	Motor neuropathy with myasthenic syndrome (from EMG)	Metastatic carcinoma	Adenocarcinoma
14	41	M	Myasthenia gravis	Thymus gland	Malignant thymoma
15	58	F	Myasthenia gravis	Thymus gland	Malignant thymoma
16	46	M	Myasthenia gravis	Bladder	Transitional cell carcinoma
17	29	F	Myasthenic syndrome with polyneuropathy (from NCV)	Spine	Large cell lymphoma
18	47	F	Myopathy involving bulbar and proximal muscles	Breast	Infiltrating ductal carcinoma
19	68	M	Polymyositis involving masseter and proximal muscles	Bone	Multiple myeloma
20	26	F	Dermatomyositis involving bulbar and proximal muscles, Optic neuritis	Nasopharynx	Poorly differentiated squamous cell carcinoma

PNPS = Paraneoplastic Syndrome of Nervous System
M = Male, F = Female

The clinical features of PNPS are summarized in Table 2.

The approximate duration of neurological symptoms in relation to neoplastic symptoms, the mode of onset, clinical course, treatment and activity of underlying malignancies are summarized in Table 3.

Table 2 Clinical features of PNPS.

Case	Clinical features
1	Mental deterioration, confusion, dysarthria, ataxia, tremor and coma.
2	Mental deterioration, psychosis and incontinence of urine.
3	Mental deterioration, bradykinesia, loss of postural tone.
4	Chaotic and irregular eye movements.
5	Ataxia of gait, upper and lower extremities.
6	Quadriparesis, loss of position sense and pinprick sensation, precipitancy of urine and constipation.
7	Bulbar and pseudobular palsy, limb weakness muscle atrophy, fasciculation and spasticity.
8	Quadriplegia, areflexia, facial diparesis, dysphagia, dysphonia, ophthalmoplegia and blindness.
9	Symmetrical limb weakness and areflexia.
10	Same as 9 plus papilledema.
11	Symmetrical paresthesia, sensory changes weakness and areflexia.
12	Same as 11.
13	Same as 9.

Table 2. (cont'd)

Case	Clinical features
14	Abnormal fatiguabilty involving, extraocular, bulbar and limb muscles and nomoreflexia.
15	Same as 14.
16	Same as 14.
17	Muscle weakness and fatiguability involving proximal limb muscles, areflexia.
18	Bulbar palsy and proximal muscle weakness.
19	Proximal muscle weakness and pain, dysphagia and trismus.
20	Skin rash, proximal muscle weakness and dysphagia, blurred vision

Table 3 Onset of PNPS, activity of malignancy at the onset, mode of onset, clinical course and treatment of underlying malignancy.

Case	Onset of PNPS	Activity of Malignancy	Mode of onset	Clinical Course	Treatment of underlying malignancy
1	4 M before	A	Subacute	Progressive	N
2	1 Yr before	A	Chronic	Progressive	Y
3	2 Yr before	A	Chronic	Progressive	N
4	1/2 M before	A	Subacute	Static	N
5	3 Yr before	A	Subacute	Static	N
6	3 M before	A	Subacute	Progressive	N
7	2 Yr after	IA	Subacute	Progressive	Y
8	1 M before	A	Acute	Progressive	Y
9	10 M before	A	Subacute	Progressive	Y
10	6 M before	A	Subacture	Progressive	Y
11	Simultaneous	A	Subacute	Progressive	N
12	5 M after	IA	Subacute	Progressive	Y
13	Simultaneous	A	Chronic	Progressive	N
14	3 Yr before	A	Chronic	Static	Y
15	3 Yr before	A	Chronic	Static	Y
16	4 M before	A	Chronic	Static	Y
17	Simultaneous	A	Subacute	Progressive	Y
18	7 M after	IA	Acute	Progressive	Y
19	Simultaneous	A	Subacute	Progressive	Y
20	2 Yr before (Myositis)	A	Subacute	Static	Y
	1 Yr after- (Optic neuritis)	IA	Acute	Static	Y

M = Month Yr = Year Y = Yes N = No
A = Active IA = Inactive
before = before the discovery of malignancy
after = after the discovery of maligancy

Pathologic study of the PNPS lesion was done in 7 cases. Autopsy was performed in 4 cases (Cases 1, 5,6 and 8). The related pathological findings of PNPS revealed: generalized cerebral edema, diffuse multifocal demyelination of cerebrum, cerebellum, brainstem and spinal nerve roots in Case 1; cerebellar atrophy, loss of Purkinji cell and granular cell layers in Case 5; subacute combined degeneration of the spinal cord in Case 6; demyelination of cranial nerves including optic nerves, and spinal nerve roots in Case 8. Sural nerve biopsy was performed in Case 9 and segmental demyelination was found. Muscle biopsy was done in Case 19 and 20 and the pathological findings revealed a classical picture of polymyositis in case 20.

The nerve conduction velocity (NCV), electromyography (EMG), with and without repetitive stimulation technique, were performed in cases with clinically suspected peripheral nervous system lesions (Cases 9-20). The NCV was prolonged in cases 9-13, and case 17. The electromyography (EMG), using repetitive stimulation technique for detection of neuromuscular junction dysfunction, was positive for myasthenia gravis in Cases 14-16 and in Cases 13 and 17, the EMG revealed classical features of myasthenic syndrome. In Cases 19-20, the EMG was diagnostic for polymyositis and in Case 18 the EMG was that of myopathy.

Cerebrospinal fluid (CSF) examination was done in Cases 1-13. The only abnormal finding was an increase of CSF protein (cases 1,2,7,9,10,11 and 13). The level of CSF protein in these cases was 100,135,63,90,198,90,122 mg/dl respectively. In case 10, who was a case of POEMS syndrome (polyneuropathy, organomegaly, endocrine changes, M protein and skin changes) there was bilateral papilledema which might be related to an increased CSF protein.

CT-Scan of brain was performed in Cases 1-5 and it showed diffuse brain edema in Case 1, cerebral atrophy in Cases 2,3,4 and cerebellar atrophy in Case 5.

The observed clinical courses of PNPS in this series were varied. Five cases (cases 1,2,5,6 and 8) died. Two of these due to causes related to the underlying malignancy. Case 5 died from massive pleural effusion. Case 6 developed increasing respiratory distress and died, but the definite cause of death could not be identified even after autopsy. Case 1 died from brain edema and brain herniation and Case 8 died from respiratory failure and associated pulmonary infection. In Case 2, the neurological symptoms initially responded to corticosteroid therapy, however she finally progressed into the vegetative stage and died. In Case 3, the parkinsonian features partially responded to levodopa therapy. In Case 9 and 10, the weakness markedly improved after treatment of the plasmacytoma. Two cases of myasthenia gravis (Cases 14 and 15) had thymectomy but after the removal of tumor, the clinical course followed the usual course of their underlying neurologic disease. In Case 16, myasthenia gravis had developed 4 months prior to the discovery of a transitional cell carcinoma of the bladder, and in this case two episodes of tumor recurrence occurred during the 3 year follow up. However, the course of malignancy had no effect on myasthenia gravis. The clinical features and EMG evidence of myasthenic syndrome in Case 17 disappeared after treatment of the lymphoma. In Case 20, the cutaneous and neurologic manifestations responded to treatment of the underlying carcinoma, but the optic neuritis developed three years later and the course of this optic neuritis was static. In Cases 3,4,11 and 13, no definite treatment of the underlying malignancies was performed and in most of them (cases 3,11 and 13) the PNPS had a progressive course. Only Case 4 had a static course. Cases 7,12,18 and 19 received specific treatment for their malignancies but the clinical courses were still progressive.

DISCUSSION

In 1958, Brain and Henson introduced the term "carcinomatous neuromyopathy" to describe various neurologic syndromes that occur in patients with malignant tumors that were not due to direct invasion or metastases[4]. Recently, the term "paraneoplastic syndrome" achieved the exalted status of a specific subject in the Index Medicus. The clinical pictures of PNPS are varied and a precise classification is often difficult since some patients may show involvement of the nervous system at several levels. Many authorities have proposed different clinicopathological classifications in various types of PNPS[5-9]. Most of these classifications are based on levels of the lesion and pathologic abnormalities. The pathological abnormalities may be degeneration, demyelination with or without inflammatory changes[5-9]. Although these neurologic disorders are separated into anatomic and pathologic categories, they often overlap. This is particularly true in our Cases 1,8,13,17 and 20, The etiology and pathogenesis of PNPS are not known. Suggestions for their causes have included autoimmune reactions, viral infections, toxins secreted by the tumor and nutritional deprivation[5,8,9]. It is possible that different mechanisms are responsible for the several types of remote effects.

Cerebral, brainstem and cerebellar involvement in PNPS include: dementia, limbic encephalitis,

Wernicke-Korsakoff syndrome, bulbar encephalitis, central pontine myelinolysis, midbrain encephalitis, subacute cerebellar degeneration, opsoclonus myoclonus-ataxic syndrome, optic neuritis-retinal degeneration, encephalomyelitis[5-9]. In this series there were two cases of dementia, one case of encephalopathy, one case of opsoclonus and one case of cerebellar atrophy. The association of hepatoma, and diffuse demyelination of the central nervous system and nerve roots is unique and, from a review of the literature, the only PNPS in malignancy of the liver previously reported is polyneuropathy[10]. Since hepatoma is rather common in Thailand the surveillance for PNPS patients with hepatoma might be worthwhile. Dementia in this series is also associated with other neurological symptoms such as psychosis, neurogenic bladder and parkinsonism. This only reflects the multiple levels of involvement in PNPS. Cerebellar atrophy and opsoclonus in this series were similar to that previously reported in PNPS. It is one of the most classical forms of presentation.

Involvement of optic nerves is rare in PNPS[11]. In this series, we have 2 cases of optic neuritis (Cases 8 and 20) and 1 case of papilledema (Case 10). The existence of true paraneoplastic optic neuritis is still controversial[5,12]. In case 8, optic neuritis occured simultaneously with Guillain-Barre' syndrome, and in Case 20 optic neuritis was detected three years after the onset of dermatomyositis. The papilledema in case 10 might be related to increase of CSF protein[13] and was not a true PNPS.

The spinal cord may be involved as well. Pathologic processes include: necrotizing myelopathy (with or without vasculitis), subacute combined myelopathy, spinal cord long tract degeneration and motor neurone disease[5-9]. In this series, subacute combined myelopathy and motor neurone disease were encountered. Motor neuron disease in this series (Case 7) presented as the classical form of amyotrophic lateral sclerosis, but the increasing in CSF protein is uncommon in classical amyotrophic lateral sclerosis[14] It is suggested that cases of motor neurone disease with high CSF protein should be investigated for the occult neoplasms. The association between malignancy and classical motor neurone disease is not strong[5,14] In our experience with 30 cases of motor neurone disease, only one case of amyotrophic lateral sclerosis was associated with breast cancer.

Disorders of peripheral nerves are the most common paraneoplastic presentations and they can manifest in several forms i.e. sensorimotor polyneuropathy, sensory neuropathy, motor neuropathy, Guillain Barré syndrome, ganglioradiculitis, relapsing-remitting polyneuropathy, mononeuritis[5-9]. In this series, two cases of sensorimotor neuropathy were associated with carcinoma of the nasopharynx and with metastatic adenocarcinoma. Two cases of subacute motor neuropathy were associated with plamacytoma. In one of these (Case 10), POEMS syndrome (polyneuropathy, organomegaly, endocrine changes, M protein, and skin changes)[13] was observed. In one case, the progressive motor neuropathy was associated with metastatic carcinoma. Guillain Barré syndrome associated with leukemia was detected in one case (Case 8). In Case 1, the overall clinical picture was one of central nervous system involvement. However, we were also able to demonstrate demyelination of spinal nerve roots at autopsy. In Case 17, the clinical picture and EMG features were diagnostic for myasthenic syndrome, but there was also a prolonged NCV which indicated the simultaneous involvement of peripheral nerves. The peripheral nerve involvement in PNPS may thus manifest either clinically or subclinically.

Neuromuscular junction disorders seen in PNPS are the myasthenic syndrome and myasthenia gravis[5-9]. The myasthenic syndrome of Eaton and Lambert is typically seen in males and in most of these patients a suspected neoplasm will eventually be found in the chest[15]. The only two cases of myasthenic syndrome in this series are female and the associated malignancies were large cell lymphoma and metastatic adenocarcinoma. One case (Case 17) had an overt myasthenic syndrome and the other case (Case 13) had only EMG evidence of the myasthenic syndrome. Myasthenia gravis is associated with tumors of the thymus in approximatelly 10%[16]. In our series of 55 case of myasthenia gravis[17], we found only 2 cases of malignant thymoma (Case 14,15). In the present series, we also have one case of myasthenia gravis whose associated malignancy was a transitional cell carcinoma of the bladder (Case 16).

Myopathy in PNPS can be classified into proximal myopathy, dermatomyositis-polymyositis, non specific degeneration and myotonia[5-9]. In this series we can detect 1 case of myopathy from carcinoma of the breast, 2 cases of dermatomyositis-polymyositis associated with multiple myeloma and carcinoma of nasopharynx respectively. The case of carcinoma of nasopharynx was rather interesting because there was also optic neuritis and this combination had never been reported previously.

The natural history and clinical course of PNPS varies. The clinical course may or may not parallel that of the underlying cancer[18]. This reflects further the difficulties in determining a cause-and-effect relationship between cancer and the various PNPS. Moreover, the persistence of paraneoplastic signs and symptoms after

tumor ablation may also result from irreversible damage to the affected distant organ system. Nerve tissue is unable to regenerate after major damage. A discordant course of the cancer and the paraneoplastic syndrome appear to be especially common with paraneoplastic neurologic abnormalities. In this series we can detect three cases of PNPS after the successful treatment of the malignancies (Cases 7,12 and 18) and these cases had a progressive course. While information concerning the response of paraneoplastic process to specific antineoplastic therapy is limited, case reports and small series would suggest that a number of syndromes are alleviated by successful treatment of the underlying malignancy. The recognized PNPS that have been noted to respond to specific antitumor therapy include : myasthenic syndrome (Eaton-Lambert syndrome), myasthenia gravis, dermatomyositis-polymyositis, neuropathy in myeloma, some cases of cerebellar degeneration and limbic encephalitis[18-19]. The PNPS in this series which showed dramatic response to treatment of their malignancies were the cases of myasthenic syndrome (Case 17), motor neuropathy in plasmacytoma (Case 9,10) and dermatomyositis (Case 20). The removal of tumor had no effect on myasthenia gravis in this series. Five cases had a progressive course after successful treatment of their malignancies (Case 2,7,12,18 and 19).

PNPS share certain general features. They can all occur without an associated neoplasm. This is important to know when speculating about their pathogenesis. Their onset and clinical course may or may not be concordant with the cancer. In addition, the same patient can have more than one PNPS at the same time, and there is considerable overlapping in the histopathology of some of the syndromes. The relationship between PNPS and cancer is thus based on the frequency of their association and the decision on the etiological significance of malignancy in temporally related PNPS are often arbitary especially in the elderly, chronic and critically ill patients who are more liable to multiple disorders. The PNPS which are reported in this paper, are by our definition clinical syndromes that are commonly encountered in patients suffering from neoplasms and these syndromes have been reported in the previous literatures. These clinical syndromes may lose the status of PNPS when their pathogeneses are uncovered.

The etiology and pathogenesis of the majority of PNPS remain unknown. Recent suggestions that autoimmunity is responsible is a recurrent theme[8,9,20,21]. However, the existence of various antibodies directed against affected parts of nervous system does not always mean that they are pathogenic and it is possible that these are only secondary phenomena responses to subtances released by neurons disintegrating for unspecified reason[8-9]. The role of neuroactive/neurotoxic subtances, and nutritional factors is always raised in disorders of unknown cause. No hard evidence exists to credit such hypothetic factors with an etiologic role in PNPS[19]. In our series the most prominent pathological findings are demyelination in the central and peripheral nervous system. Since many acquired demyelinating processes in adults are widely held to be immunologically mediated[22,23,24], we believe that the demyelinating process observed in our cases may have such a mechanism.

From our data, 13 out of 20 cases of PNPS were observed before the recognition of their malignancies. Therefore if clinicians become familar with PNPS and the fact that they will commonly precede recognition of the malignancy, this will lead to a search for tumors in such patients. However, the cancer may be so small as to defy efforts to expose its presence. Studies which are rational in attempting to find "occult" neoplasms in patients with PNPS include: a thorough physical examination that should be repeated periodically and which includes, breast, nasopharyngeal, pelvic and rectal examinations. A chest x-ray, and radiographic skeletal survey are suggested in an effort of to find pulmonary malignancy and solitary plasmacytoma. An elevated CSF protein level[25] is a good indicator for malignancy work-up in a case of suspected PNPS. It is common in PNPS (7 out of 13 cases in this series). A complete blood count, serum immunoelectrophoresis, and other tumor markers (carcinoembrionic antigen, α feto protein) may disclose an associated hematologic malignancy, plasma cell dyscrasia or evidence of carcinoma. In the absence of systemic symptoms, it seems that an exhaustive battery of diagnostic tests beyond the suggested investigations will rarely detect the "occult" cancer but a continuous follow up will.

SUMMARY

Paraneoplastic syndromes of the nervous system (PNPS) are disorders of unknown cause that occur in patients with occult or identifiable malignancy. Their manifestations are protean. Data concerning 20 patients with PNPS are presented. The most common PNPS were syndromes involving the peripheral nervous system and muscle, these included 6 cases of peripheral neuropathy, 3 cases of myosthenia gravis, 1 case of myastlenic syndrome, 1 case of myopathy and 2 cases of polymyositis. The central nervous system manifestations were: 1 case of encephalopathy, 2 cases of dementia, 1 case of cerebellar atrophy, 1 case of opsoclonus, 1 case of subacute

combined degeneration of the spinal cord, and 1 case of amyotrophic lateral sclerosis. The most common pathological finding in this series was central and peripheral demyelination. The underlying malignancies were: 4 cases of breast cancer, 2 cases each of lung cancer, leukemia, plasmacytoma, nasopharyngeal carcinoma, malignant thymoma and metastatic tumor and 1 case each of lymphoma, bladder carcinoma, multiple myeloma and hepatocellular carcinoma. The most common abnormality in routine investigation was an elevated CSF protein. The clinical course, response to therapy of these cases, the pathogenesis as well as clinical investigation of this entity are discussed.

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