Autonomic neuropathy and carcinoma of the lung

M. NISAR AHMED,* MB, BS, FRCP[C]; STIRLING CARPENTER,† MD

Summary: A patient who died from oat-cell carcinoma of the lung had had abdominal pain and obstipation. Autopsy revealed autonomic neuropathy limited to the gastrointestinal tract, which was considered to be related to carcinoma as a remote effect. This interpretation was further supported by the presence of Wallerian degeneration of the dorsal columns. Autonomic neuropathy involving the gastrointestinal tract in association with malignant disease has not been previously described.

Résumé: *Neuropathie autonome et carcinome pulmonaire*

Un malade qui est décédé d'un carcinome pulmonaire à petites cellules (en "grain d'avoine") avait souffert de douleurs abdominales et de constipation rebelle. On découvrit à l'autopsie une neuropathie du système autonome limitée au tractus gastrointestinal et qu'on a considéré comme un effet éloigné, relié au carcinome. Cette interprétation était du reste confirmée par la présence de dégénérescence wallérienne des colonnes dorsales. C'est la première fois qu'on trouve dans la littérature un cas de neuropathie autonome impliquant le tractus gastrointestinal associé à une pathologie maligne.

Acquired autonomic neuropathy limited to the gastrointestinal tract is rare. We report such a case with pathological verification; the cause is unknown, but the neuropathy was associated with a carcinoma of the lung. To the best of our knowledge the picture we report has not been previously described.

Case report

A 58-year-old man was admitted to hospital with a 5-month history of abdominal pain and constipation. Squeezing pain was the first symptom noted; it would start in the middle of the abdomen, peak in about an hour and subside in several hours after waxing and waning. It had no relation to meals or posture. Constipation developed later and gradually worsened until he passed soft stools only once every 3 to 7 days. During this period he became anorectic, vomited frequently and began to lose weight; by the time of admission he had lost 18 kg.

He was emaciated. Irregular lumps, thought to be impacted feces, were palpable in both lower quadrants of the abdomen. Hemogram, biochemistry findings, electrocardiogram and chest radiograph were normal. A plain film of the abdomen revealed barium remaining from an examination done at another hospital 6 to 8 weeks before this admission. In spite of fluid diet, cathartics, enemas and sigmoidoscopic manipulation his colon could not be cleared of feces for a barium enema examination.

Supportive therapy failed to relieve his symptoms. Laparotomy revealed, as the only abnormality, dilatation of the colon with decreased peristalsis; no obstructive lesion was seen. A transverse colostomy was done and a segment of the colonic wall removed for pathological examination.

The patient's recovery was slow and on reinstitution of oral feeding, nausea and abdominal pain recurred. Little fecal matter collected at the colostomy. Further extensive investigations and repeated physical examination failed to reveal a cause for his ailment. No detailed sensory findings were recorded. He became progressively more sick and intermittent intravenous alimentation was necessary. His subsequent hospital course was complicated by recurrent episodes of pneumonia and terminally by a gram-negative septicemia. He died approximately 4 months after admission and 9 months after the onset of his illness.

Pathologic findings

Biopsy: The colonic biopsy showed infiltration of the myenteric and submucous plexuses by large numbers of plasma cells and, to a lesser extent, lymphocytes (Fig. 1). However, numerous autonomic neurons were seen and no definite loss of neurons was demonstrated. The degree of infiltration varied considerably from plexus to plexus, some areas appearing almost normal. The smooth muscle coats were unaffected.

Autopsy: Segmental dilatation of the small and large intestines with some thinning of the wall was noted. No obstructive lesion was found. Many histologic sections from the esophagus to the colon showed abnormalities of the myenteric and submucous plexuses. Compared with the biopsy, these sections contained fewer inflammatory cells, more fibrous tissue within the plexuses and more Schwann cells (Fig. 2). A definite loss of axonal fibres was demonstrated with Bodian stain.

Formalin-fixed blocks of the colon were processed for electron microscopy. Electron micrographs showed a striking decrease in the numbers of axons in the bundles of the myenteric plexus. Schwann cell processes were folded upon themselves and one another and appeared considerably more numerous than in normal tissue. Plasma cells were noted; one, beneath the basement membrane of the plexus, was separated from a neuron by only a thin layer of Schwann cell cytoplasm (Fig. 3). The neurons did not show any striking morphologic abnormalities that could not

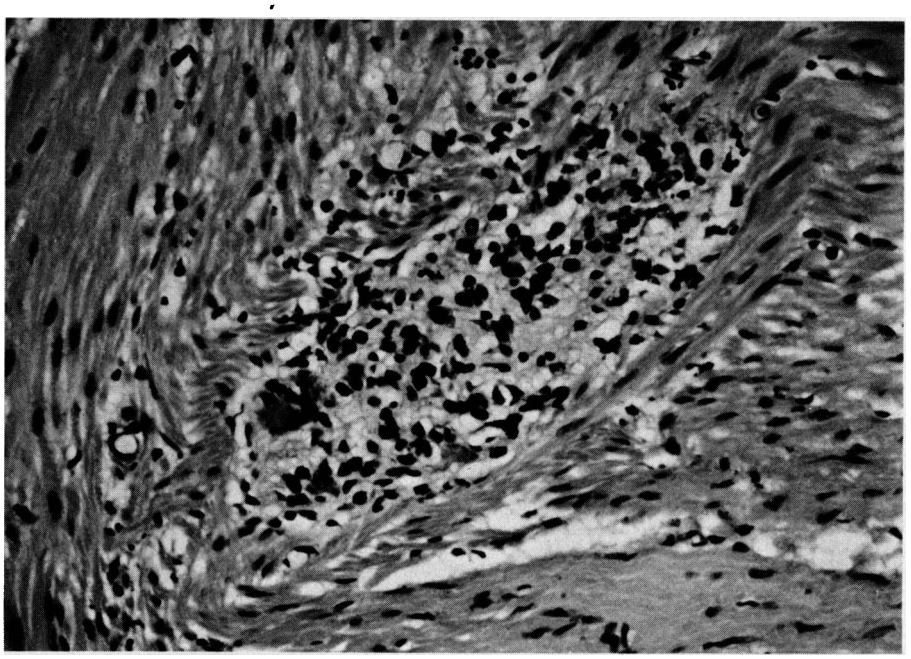

FIG. 1—Colonic biopsy: infiltration of myenteric plexus by plasma cells and lymphocytes. Well preserved neuron at left (hematoxylin-eosin; x250).

From the department of pathology, McGill University, Montréal

*Assistant professor of pathology
†Associate professor of pathology

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Reprint requests to: Dr. M.N. Ahmed, Department of pathology, McGill University, 3775 University St., Montréal, Qué. H3A 2B4

be attributed to postmortem artefact.

Adherent to the right mainstem bronchus and the adjacent part of the trachea was a hard, greyish-white tumour mass (dimensions, 3 x 3 x 2 cm) composed of metastatic oat-cell carcinoma in lymph nodes (Fig. 4). An extensive search for a primary lesion in the bronchial tree was unsuccessful. No other metastases were found. Both lungs showed extensive bronchopneumonia.

The cervical spinal cord showed a symmetric loss of myelinated fibres in the dorsal columns; the brain showed no abnormality. The psoas muscle contained groups of angular atrophic fibres. Dorsal root ganglia, peripheral nerves and sympathetic ganglia were not examined.

The remainder of the autopsy findings were noncontributory. Death was attributed to septicemia secondary to bronchopneumonia.

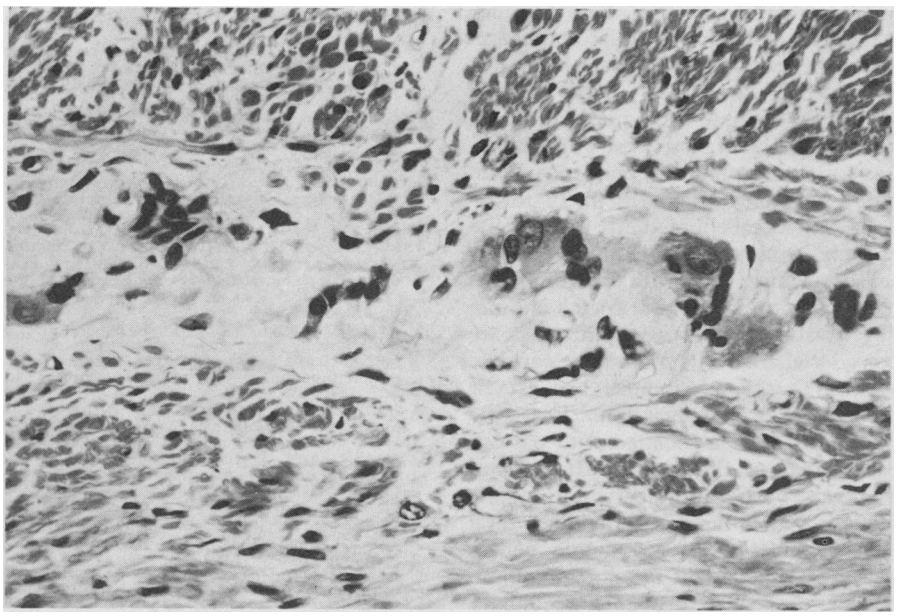

FIG. 2—Myenteric plexus from colon at autopsy: increase in fibrous tissue and number of Schwann cells; decrease in number of inflammatory cells. Well preserved neurons at right (hematoxylin-eosin; x400).

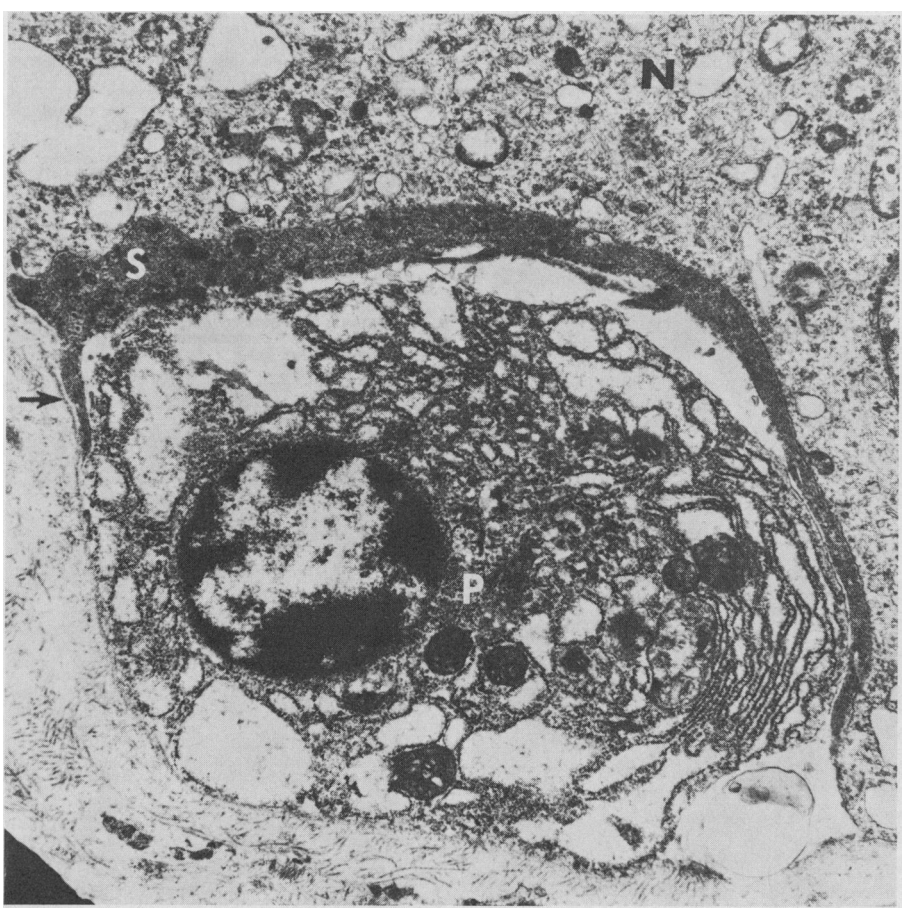

FIG. 3—Part of cytoplasm of neuron (N) from myenteric plexus, dense Schwann cell process (S) and plasma cell (P) lying beneath basement membrane (arrow) of plexus (reduced 25% from x13 000).

Discussion

The total picture in this patient was unusual. His intestine was dilated, apparently because of an inflammatory neuropathy affecting the autonomic plexuses of the entire gastrointestinal tract. The damage appears to have been more severe to the nerve cell processes than to the neurons themselves. The only other abnormality found in the nervous system was Wallerian degeneration of the dorsal columns, which was probably secondary to disease of the sensory ganglia, although the patient was not known to have had any pertinent signs or symptoms. The psoas muscle showed changes consistent with denervation. In addition, there was an oat-cell carcinoma of the lung. The primary site was not found despite extensive search, but this is not unusual for this type of carcinoma. No metastases were found outside the bronchial lymph nodes.

The unusual findings in this case were those of an acquired autonomic neuropathy. In regard to the cause, conditions associated with autonomic neuropathy should be considered.

Chagas' disease is known to involve the autonomic nervous system with inflammatory infiltrates and loss of ganglion cells.[1,2] Hypertrophy and then dilatation of the gastrointestinal tract follow. Our patient was not known to have ever been in an endemic area, and the autopsy did not reveal any other lesions that could be interpreted as evidence of Chagas' disease.

The most common inflammatory neuropathy in North America is the Guillain-Barré syndrome or idiopathic polyneuritis. In many cases there is evidence of autonomic involvement, such as loss of vascular reflexes, anhidrosis and disorders of pulse or blood pressure.[3] Lymphocytic infiltrates have been described in autonomic ganglia and rami communicantes.[3,4] These patients have not had prominent abdominal complaints. Idiopathic polyneuritis is thought to be caused by abnormal immune responses, mainly because morphologically similar demyelinative lesions can be produced in animals by injection of minced peripheral nerves in Freund's adjuvant.[3] This experiment has also been done with sympathetic nerves, and in animals thus treated, physiologic abnormalities in blood vessel response could be demonstrated by careful testing.[5] Half of these animals showed mild infiltrates

of mononuclear cells into the sympathetic ganglia. The clinical course and the lesions of both idiopathic and experimental allergic polyneuritis appear different from those of our patient.

Autonomic symptoms may be prominent as part of some generalized neuropathies of adult life such as diabetic[6] and amyloid neuropathy;[7] our patient had no evidence of these diseases.

A number of cases have been reported under the heading of acute pandysautonomia.[8-15] In most of these patients the only neurologic deficits were related to the autonomic nervous system. However, the majority recovered completely or partially after several months. Most had gastrointestinal symptoms with constipation. Sural nerve biopsy findings varied from normal[9] to an increase in the number of miniature unmyelinated axons,[8] which was interpreted as consistent with regeneration of axons. Inflammatory infiltrates were not seen. Four cases of pandysautonomia have been reported in association with malignant disease, three with small-cell bronchogenic carcinoma[14,16,17] and one with an adenocarcinoma of the pancreas.[18] An autopsy in one patient with a bronchogenic carcinoma showed no morphologic abnormality of the autonomic nervous system.[14] The presenting symptoms of these four patients were unlike those of our patient.

Three patients with carcinoma have been reported who had a similar clinical picture to that of our patient, presenting with constipation and colicky abdominal pains.[19,20] In each case metastases were found in the celiac axis at operation and in one, carcinomatous infiltration of sympathetic postganglionic fibres below the semilunar ganglion was seen at autopsy.[19] In our patient there was no carcinomatous infiltration of the celiac axis, and, if his autonomic neuropathy is to be related to the carcinoma, it must be considered as a remote effect.

Abnormalities of the neuromuscular system in patients with carcinoma, unrelated to metastases, have been documented.[21] The most clearly defined syndromes include a unique disorder of neuromuscular transmission (the Eaton-Lambert syndrome),[22] a polioencephalopathy that is particularly likely to affect the cerebellum and may show chronic inflammatory features,[23] and a sensory neuropathy with loss of dorsal root ganglion cells and dorsal column degeneration.[24,25] These syndromes are considered to be in some way causally related to the carcinomas because of their statistical association. They are most frequently associated with oat-cell carcinomas of the lung.[26,27] In the numerous reports of these remote effects of carcinoma there is an almost total lack of mention of autonomic neuropathy. In our patient the dorsal column degeneration was probably secondary to disease of the dorsal root ganglia, such as one might see in a sensory neuropathy associated with carcinoma. Although he did not have the lightning pains and paresthesias that frequently trouble these patients, he may have had a mild form of such a paracarcinomatous neuropathy.

Because neurologic abnormalities, as a remote effect, may occur in patients with carcinomas, particularly oat-cell carcinoma, it is tempting in this case to assume a causal relation between the autonomic neuropathy and the carcinoma. We expect that confirmatory evidence will be found in other cases of this association while we await unravelling of the pathogenetic mechanisms.

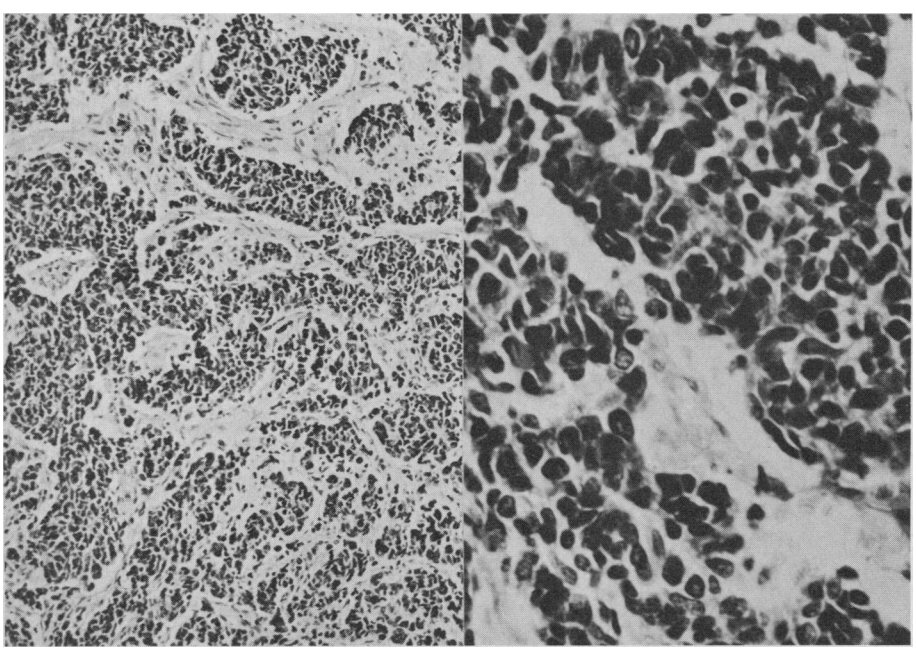

FIG. 4—Metastatic oat-cell carcinoma in peribronchial lymph node, composed of sheets and ribbons of malignant cells showing pleomorphism, scanty cytoplasm and hyperchromatic nuclei (hematoxylin-eosin: left, x125; right, x400).

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