Short report

Acute myeloradiculitis due to cytomegalovirus as the initial manifestation of AIDS

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SUMMARY A 26 year old male intravenous drug abuser presented with rapidly progressive paraplegia and total incontinence. CSF examination showed elevated protein level and pleocytosis. HIV testing was positive. Anti CMV titres were mildly elevated in serum and CSF. Death occurred 26 days after the onset of neurological signs. Necrotic and inflammatory lesions with numerous inclusion bodies characteristic of CMV were found in the roots of the cauda equina, conus terminalis and lumbar segments of the spinal cord. CMV subependymal encephalitis and HIV encephalitis were also present.

Cytomegalovirus (CMV) infection is one of the main criteria for the diagnosis of the Acquired Immunodeficiency Syndrome (AIDS) due to the human immunodeficiency virus (HIV).¹ It is usually diffuse² and in many cases is the immediate cause of death.³ CMV involvement of the nervous system usually produces encephalitis.⁴ This latter had been found in about 25% of CNS lesions in AIDS in a number of necropsy series.^{2,4,5}

Since 1984 six cases of the so-called CMV "induced demyelination" in the roots and spinal cord⁶ have been reported in AIDS patients with neurological symptoms referred to as "Guillain-Barré syndrome",⁷ "polyradiculopathy",⁸ "polyneuropathy",⁹ "spinal cord syndrome"¹⁰ and "polyradiculoneuropathy".¹¹ These cases were recently grouped together and classified by Dalakas and Pezeshkpour¹² as "progressive inflammatory polyradiculoneuropathies presenting as cauda equina syndrome".

The present paper describes a further clinicopathological case in which the neurological syndrome was the initial manifestation of AIDS.

Case report

A 26 year old intravenous drug abuser, Algerian male, was admitted to hospital with a 3 day history of lumbar pain (day 1), weakness of right leg (day 2) and urinary retention (day 3). Myelography was normal. CSF contained 441 mg/dl protein, 2.60 mmol/l glucose, 260 RBCs and 500 WBCs (70% polymorphs and 30% lymphocytes)/mm³.

On admission, temperature was 38°C and mild lymphadenopathy was noted. The patient was alert and oriented. Examination of the cranial nerves and upper extremities was normal. Monoplegia with areflexia and diminished pinprick and position sense was observed in the right leg. Plantar responses were equivocal on the right and flexor on the left. Over a 10 day period the deficit extended to a complete flaccid paraplegia with bowel and bladder incontinence. CT of the brain and fundoscopy were normal. A second CSF sample (day 11) contained 170 mg/dl protein, 2.60 mmol/l glucose 55 RBCs and 145 WBCs (60% lymphocytes, 25% polymorphs and 15% monocytes)/mm³. Serum titres were 1/10,000 for HIV, 1/160 for CMV, and 1/6,400 for herpes simplex virus (HSV); CSF titres were 1/100 for HIV, 1/8 for CMV and 1/160 for HSV. Tests were negative for HBs antigen (whereas HBs and HBc antibodies were positive) and cryptococcal antigen; VDRL, bacterial, fungal mycobacterial cultures were negative. A biopsy of muscle and peripheral nerve performed at day 16; the specimen showed no significant changes on frozen, paraffin embedded or semi-thin sections and teasing preparations. Immunostaining for HIV was negative.

Subsequently the patient developed oral candidiasis; gastroscopy showed erythematous gastritis without oesophageal

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Fig 1 (a) Ependymal lining of the lateral ventricle. Infected ependymal cell protruding into the ventricular lumen. (H and E, $\times 1100$). (b) Necrotic lesion involving myelinated axons with better preservation of axons at the periphery (arrow). (Bodian-Luxol $\times 300$). (c) Polymorphic inflammatory infiltrate in a necrotic lesion, around a blood vessel. (H and E, $\times 300$). (d) Cytomegalic cells with intranuclear inclusion bodies in the leptomeningeal space. (H and E, $\times 480$). (e) (e) CMV inclusion bodies in possible Schwann cells (arrows) (H and E, $\times 1000$). (f) Anterior horn of the lumbar segment of the spinal cord. Marked central chromatolysis (H and E, $\times 1000$).

lesion. He became progressively drowsy. Untreatable hiccup appeared on day 18, horizontal nystagmus in lateral gaze on day 21 and left facial paresis on day 24. Repeat CT of the brain was normal. Twenty-six days after onset of the illness the patient developed severe enterocolitis, became dehydrated, hypotensive and died.

Pathological examination

Post mortem examination was limited to brain, spinal cord and roots. On *gross examination* the brain weighed 1420 g and was externally normal. The leptomeningeal blood vessels were normal. Coronal slices showed greyish, ill defined discolouration of the hemispheric white matter most markedly in the parieto-occipital regions. The brainstem, cerebellum spinal cord and roots did not show significant changes.

Microscopical examination After fixation, blocks were taken from many regions of the cerebral hemispheres, cerebellum, brainstem, spinal cord, roots and ganglia and embedded in paraplast or in celloidin. Sections were stained with haematoxylin and eosin, Loyez stain for myelin, Masson trichrome and Bodian silver impregnation combined with Luxol fast blue. Immunostaining was performed on paraffin-embedded specimens by the peroxidase-antiperoxidase (PAP) technique using a polyclonal antiserum raised against CMV (Polyscience, France).

Histological examination of the brainstem and cerebral hemispheres showed extensive loss of the ependymal lining, granular ependymitis and presence of microglial nodules in the subependymal layer. Large cytomegalic cells were present and some of them protruded into the ventricular lumen (fig. a). In addition, there was diffuse, ill defined pallor of the hemispheric white matter with reactive glial proliferation. Small subcortical foci of necrosis containing macrophages and occasional multinucleated giant cells, microglial nodules and mineralisation of blood vessels were suggestive of HIV encephalitis.²

Severe changes were found in the cauda equina and lower segment of the spinal cord and consisted of multiple small foci of recent necrosis involving roots and subpial regions of the conus medullaris and lumbar spinal cord, with myelin loss and severe reduction of the number of axons. These latter, however, appeared relatively spared at the periphery of the lesions (fig. b). Inflammatory reaction, which included neutrophils, plasma cells, lymphocytes and some histiocytes and macrophages (fig. c) was present within the areas of necrosis as well as around the blood vessels and in the leptomeninges; in the same areas CMV intranuclear inclusion bodies could be seen (fig. d). Though not all inclusion body containing cells could be identified, many of them had the features of Schwann cells (fig. e). In the lower segments of the spinal cord, most anterior horns cells showed marked central chromatolysis (fig. f).

The thoracic and cervical segments of the cord were unremarkable. Examination of the spinal ganglia and extradural peripheral nerves did not show any necrotic, demyelinating or inflammatory change. No multinucleated giant cells were found in the spinal cord and roots; HSV inclusion bodies were not observed at any level of the central nervous system or in the roots.

Immunocytochemical methods for CMV stained positively the cytoplasm of large ependymal and sub-

ependymal cells as well as some in the spinal roots and leptomeninges of the cauda equina and inferior part of the cord. No staining was observed in the deep white matter, basal ganglia, spinal ganglia and extradural part of the spinal roots.

Discussion

A variety of lesions of the central and/or peripheral nervous system have been described in patients with HIV infection.¹²⁻¹⁴ In the present case, rapidly progressive flaccid paraplegia could be related to necrotic and inflammatory lesions of the lower segments of the spinal cord and intra-dural lower spinal roots due to direct infection by the CMV. These features distinguish this myeloradiculopathy from Guillain-Barré syndromes secondary to immunological disorders of spinal roots and peripheral nerves, which have already been observed in AIDS patients.^{12 14 15}

Despite the high HSV serum titres, there was no evidence on the numerous specimens examined of concomitant HSV infection of the CNS as described by Yanagisawa *et al*¹⁶ and Tucker *et al*.¹⁷ Lesions of subacute encephalitis with multinucleated giant cells characteristic of HIV infection of the CNS were present in the hemispheric white matter but could not be observed in the cauda equina and spinal cord. Association of HIV and CMV infection in AIDS have been already described by Kleihues *et al*¹⁸ who suggested a synergic action of these viruses at the origin of brain demyelinating lesions. Such a combined action of both viruses had also been proposed at the origin of demyelinating lesions of the peripheral nervous system.^{12 14} However, since, in the present case, HIV infection appeared to be limited to the brain, it is possible that CMV infection involving the Schwann cells be sufficient *per se* to cause the lesions of spinal cord and roots.³

Six cases of CMV myeloradiculopathy have been reported since 1984^{6 11} with neuropathological features in spinal cord and roots similar to those described in the present case. CMV infection of ependymal cells was also observed by Eidelberg *et al*⁸ who proposed that such "infected ependymal cells may detach, travel along CSF pathways and implant caudally". This hypothesis could account for the lumbosacral predilection and intrathecal localisation of the inflammatory lesions.

The clinical features in those cases and the present one were remarkably similar (table) and included: pain at onset (lumbar and/or radicular), rapid progression to flaccid paraplegia, absence of major sensory deficit, early and severe global sphincter dysfunction and acute aggravative course leading to death in a few weeks. The only case with prolonged evolution was that of Moskowitz *et al*⁶ in which CMV invasion seemed to be limited for a long time to the nervous

Table Clinical features in the present case and the previously reported ones of CMV myeloradiculopathy

	Age* (yr)	Previous infections	Pain at onset	Paraplegia occurrence	Sensory loss	Sphincterian dysfunction	Duration*
Moskowitz <i>et al</i> ⁶ (case 3)	34	<i>P. Carinii</i> HSV	+	1, 5 week	stocking gloves ?		24 weeks
Bishopric <i>et al</i> ⁷ (case 1)	41	<i>P. Carinii</i> candidiasis HSV	+	1 week	0	?	3 weeks
Eidelberg <i>et al</i> ⁸ (case 1)	34	<i>P. Carinii</i> candidiasis CMV	+	2, 5 weeks	perianal genital subjectiv trouble	retention incontinence retention	4, 5 weeks
Jeantils <i>et al</i> ⁹	43	<i>P. Carinii</i>	+	2, 5 weeks	0	incontinence	8 weeks
Singh <i>et al</i> ¹⁰ (case 1)	37	<i>P. Carinii</i>	0	2, 5 weeks	0	incontinence	4 weeks
Behar <i>et al</i> ¹¹	33	<i>P. Carinii</i> candidiasis	0	2, 5 weeks	0	retention	7, 5 weeks
Present case	26	0	+	2 weeks	stockings	retention incontinence	4 weeks

*Duration of illness from presentation to death.

system. However, unlike all the other cases previously reported in which this complication appeared late in the course of the disease, subsequently to various opportunistic infections such as *Pneumocystis carinii* pneumoniae, HSV infection and/or candidiasis, in the patient described here CMV myeloradiculopathy was the initial manifestation of AIDS.

All cases had meningitis with pleocytosis (50 to 1140 cells) of polymorphonuclear predominance (57% to 97% in the six cases assayed). Viral tests for CMV were usually of poor help, CMV grew from blood or urine in one single case⁹ and blood titres were positive in two cases: 1/256¹⁰ and 1/32.¹¹ CMV was cultured from CSF in one case⁹ only.

The recent finding that 9-(1,3-dihydroxy-2 propoxymethyl)guanine (DHPG) (Ganciclovir)^R is effective in the treatment of CMV infections⁹ has made the early diagnosis of this myeloradiculopathy important. Since viral tests for CMV usually fail to demonstrate active CMV infection of the nervous system (cf. supra), the diagnosis of CMV acute myeloradiculitis has to be made, and the treatment started, on the suggestive, rapidly progressive cauda equina clinical syndrome only.

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Armand Trousseau and Parkinson's disease

Armand Trousseau (1801–1867) was a distinguished French physician who worked in the Hôpital St Antoine in Paris. Best known for his description of venous thrombosis as a possible signal of a visceral cancer, he observed this in himself, confirming his suspicion of gastric carcinoma.

Of neurological interest and importance is his contribution to Parkinson's disease in his *Lectures on Clinical Medicine*.¹ He described (1861, later translated in 1868) rigidity, a sign Parkinson did not pay attention to, and he explained the *scelotyrbie festinans*: “as his centre of gravity is thus displaced, he is obliged to run after himself, as it were, so that he keeps trotting and hopping on.” Trousseau also described the progressive slowing of repeated hand opening, the first clear account of bradykinesia. Although James Parkinson had said “the senses and intellects being uninjured”, Trousseau commented: “the intellect. . . gets weakened at last; the patient loses his memory, and his friends notice soon that his mind is not as clear: precocious caducity sets in.” Trousseau was a realist. He had, he said, not cured a single patient with medicaments; pneumonia was the common ending.

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