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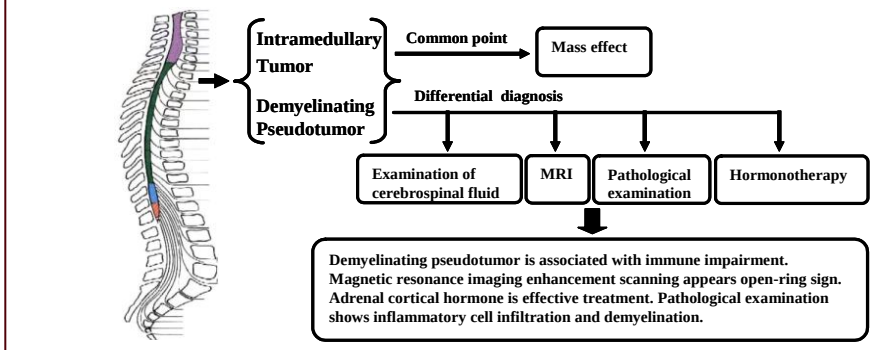
Imaging and clinical properties of inflammatory demyelinating pseudotumor in the spinal cord

Ying Wang, Min Wang, Hui Liang, Quntao Yu, Zhihui Yan, Min Kong

Department of Neurology, Yantai Shan Hospital, Yantai 264000, Shandong Province, China

Graphical Abstract



Abstract

Inflammatory demyelinating pseudotumor usually occurs in the brain and rarely occurs in the spinal cord. On imaging, inflammatory demyelinating pseudotumor appears very similar to intramedullary tumors such as gliomas. It is often misdiagnosed as intramedullary tumor and surgically resected. In view of this, the clinical and magnetic resonance imaging manifestations and the pathological features of 36 cases of inflammatory demyelinating pseudotumor in the spinal cord were retrospectively analyzed and summarized. Most of these cases suffered from acute or subacute onset and exhibited a sensorimotor disorder. Among them, six cases were misdiagnosed as having intradullary gliomas, and inflammatory demyelinating pseudotumor was only identified and pathologically confirmed after surgical resection. Lesions in the cervical and thoracic spinal cord were common. Magnetic resonance imaging revealed edema and space-occupying lesions to varying grees at the cervical-thoracic junction, with a predominant feature of non-closed rosette-like forcement (open-loop sign). Pathological examination showed perivascular cuffing of predominantly dense lymphocytes, and demyelination was observed in six of the misdiagnosed cases. These results suggest that tumor-like inflammatory demyelinating disease in the spinal cord is a kind of special demyelinating disease that can be categorized as inflammatory pseudotumor. These solitary lesions are easily confused with intramedullary neoplasms. Patchy or non-closed reinforcement (open-ring sign) on magnetic resonance imaging is the predominant property of inflammatory myelinating pseudotumor, and inflammatory cell infiltration and demyelination are additional palogical properties.

Key Words

neural regeneration; spinal cord injury; spinal cord; neoplasms; demyelinating disease; magnetic resonance imaging; image enhancement; multiple sclerosis; gliomas; inflammatory cell infiltration; neuroregeneration

Ying Wang, Master, Chief physician, Master's supervisor.

Corresponding author: Hui Liang, Master, Chief physician, Master's supervisor, Department of Neurology, Yantai Shan Hospital, Yantai 264000, Shandong Province, China, wangyrq@163.com.

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INTRODUCTION

At present, demyelinating diseases that attack once and clinically involve only one region are known as “clinically isolated syndrome”. On MRI, these diseases mostly manifest as a single, solid and obvious space-occupying lesion surrounded by edema and a ring-like reinforcement shadow. It is difficult to distinguish such lesions, which were first reported by van der Velden in 1979[1], from intramedullary tumor. They are easily misdiagnosed as tumors such as gliomas, and are definitively diagnosed by pathological examination after surgical resection, which causes unnecessary damage to patients. Lee *et al* [2] conducted a retrospective analysis of 212 patients diagnosed with spinal tumors. Their postoperative pathological findings revealed that nine patients did not have spinal tumors; of these, four had demyelinating disease, two had sarcoidosis, two had amyloid angiopathy, and one had inflammation of unknown etiology.

Thus, demyelinating disease accounted for the largest proportion of misdiagnosed cases. It was reported on 38 patients that underwent spinal biopsy, in whom the etiology of myelopathy remained unknown[3]. Among diagnoses following biopsy, inflammatory demyelinating disease and sarcoidosis were the most common diseases, accounting for 34%, while tumors were the cause of disease in up to 21%. Thus, exploring this kind of special demyelinating pseudotumor from the perspectives of clinical manifestations, medical examinations, MRI features, and pathological features would be important for guiding clinical practice[4]. Then, what are the clinical, imaging and pathological characteristics of demyelinating pseudotumor in the spinal cord and how might we identify demyelinating pseudotumor in the spinal cord?

With the aim of reducing the clinical misdiagnosis rate, we retrospectively analyzed and summarized the clinical manifestations, laboratory findings, MRI features and follow-up results of cases with tumor-like inflammatory demyelinating disease in the spinal cord misdiagnosed as intramedullary tumors.

RESULTS

Quantitative analysis and baseline data of subjects

Thirty-six patients with tumor-like inflammatory demyelinating disease in the spinal cord, consisting of 13 males and 23 females, aged 38.7 ± 5.2 years, were included in this study. Eleven had a previous history of immune system diseases, including systemic lupus erythematosus (*n* = 3), rheumatoid arthritis (*n* = 5), hyperthyroidism (*n* = 1), infectious arteritis (*n* = 1), and hypothyroid (*n* = 1). All of these patients were included in the final analysis, without dropouts or loss.

Clinical manifestations, sensory, motor and autonomic disorders of patients with tumor-like inflammatory demyelinating disease in the spinal cord

Among the 36 patients, acute onset (reaching a peak within 1 week) occurred in nine patients, sub-acute onset (reaching a peak from 1 to 4 weeks) occurred in 15 patients, and chronic onset occurred (reaching a peak after 1 month) in 12 patients. Twelve patients suffered from upper respiratory tract infection and diarrhea before disease onset, and the remaining 24 patients suffered from their first episode of tumor-like inflammatory demyelinating disease in the spinal cord without any predisposing factors. The first symptoms in these patients included limb numbness (*n* =18), asymmetric limb weakness (*n* = 7), thoracic and abdominal zonesthesia (*n* = 8), Lhermitte’s syndrome (*n* = 13), urinary retention (*n* = 5), and corticospinal tract lesion (*n* = 16). Muscular atrophy was observed in 11 patients, but there were no eyesight or hearing disorders.

Movement disorders: among 24 patients with movement disorders, nine had asymmetric tetraplegia, 12 had asymmetric double lower limb paralysis and three had unilateral limb paralysis.

Sensory disorders: all 36 patients presented with a superficial sensory disorder, and a cl-

ear asymmetry conduction bundle sensory plane was dynamically observed. Twelve patients had combined sensory hypersensitivity, 11 patients had thoracic and abdominal zonesthesia, 15 patients had deep sensory disorders, and nine patients had Lhermitte's syndrome.

Autonomic nervous dysfunction: five patients had urinary retention and six patients had limb or body sweating disorder.

Assessment of disability in patients with tumor-like inflammatory demyelinating disease in the spinal cord

The degree of disability in patients was evaluated using the international Expanded Disability Status Scale (EDSS) by professional staff. Nine patients were scored within the range 1.0–3.5 points, 20 patients were scored 3.5–7.0, and seven patients scored > 7.0 points.

Cerebrospinal fluid examination suggested immune system damage

Nineteen patients presented with slightly increased cerebrospinal pressure (1.86–2.16 kPa). The number of white blood cells was normal in 12 patients, but was increased (1.1–5.6 × 10^7/L) in 24 patients. Protein level was normal in 21 patients while hypertension (0.43–1.70 g/L) was observed in 15 patients. The IgG level was slightly increased in 17 patients, with elevated IgM observed in eight patients.

Changes in visual- and brainstem auditory-evoked potentials in patients with tumor-like inflammatory demyelinating disease in the spinal cord

Visual-evoked potentials and brainstem auditory-evoked potentials were normal in all patients before methylprednisolone and immunoglobulin treatment. On electromyography, 25 patients were normal; slowed nerve conduction velocity was observed in 11 patients and decreased wave F amplitude and rate were seen in three patients.

Magnetic resonance imaging characteristics of patients with tumor-like inflammatory demyelinating disease in the spinal cord

Lesion distributions: 12 patients had lesions in the cervical cord (Figure 1), 17 patients had lesions in the thoracic cord (Figure 2), and seven patients had lesions in the cervical-thoracic cord (Figure 3). Lesions mainly involved the white matter. The gray matter was simultaneously involved in six patients and no bleeding or cavities was seen. Twenty-five patients had single lesions (Figures 1, 3), eight patients had two lesions and three patients had three lesions (Figure 2). Six patients who had single lesions received surgery.

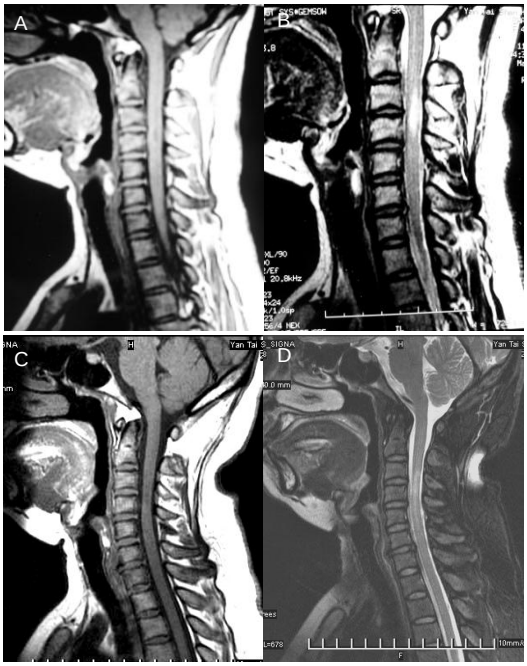

Figure 1 Imaging changes in the solitary lesion in the cervical spinal cord of a 38-year-old female patient with tumor-like inflammatory demyelinating disease before and after hormone therapy.

(A) Sagittal fluid attenuated inversion recovery (FLAIR) T1WI scan showing an intramedullary lesion in cervical segments 3–4, with a long T1 signal before hormone therapy. (B) Sagittal fast spin echo (FSE) T2WI showing a lesion with long T2 signal before hormone therapy. (C) Sagittal FLAIR T1WI scan showing that the lesion was not visible and cervical cord atrophy in cervical segments 3–4 after hormone therapy. (D) Sagittal FSE T2WI showing the lesion was visible and cervical cord atrophy after hormone therapy.

Lesion signals: 25 patients showed uniform long T1 signals representing intramedullary lesions, while 11 patients presented with equal T1 signals; 26 patients showed homogeneous long T2 signals, and 10 patients presented with uneven long T2 signals. The intramedullary lesions showed as uniform equal or long T1 signals or long T2 signals (through plain scanning, three patients presented with equal or long T1 or T2 signals and the spinal cord near the lesions was thickened and swollen; Figure 3).

T1-weighted imaging (T1WI) enhancement scanning: After intravenous administration of enhanced contrast agent gadolinium-diethylenetriaminepentaacetic acid (Gd-DTPA; 0.2 mL/kg), patchy enhancement was observed in 11 patients (Figures 2C, 3C), trans-axial annular enhancement in 25 patients, and open-ring enhancement was observed in 11 patients (Figures 2D, 3D), but no abnormality was found by skull MRI.

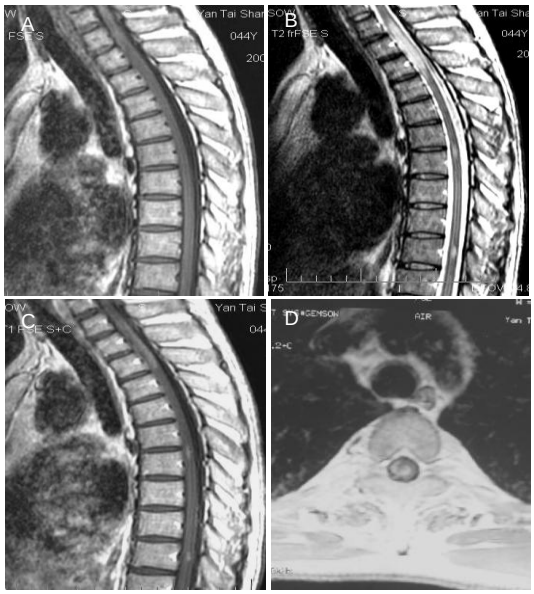

Figure 2 Magnetic resonance imaging results of thoracic spinal cord of a 44-year-old male patient with tumor-like inflammatory demyelinating disease, who complained of lower extremity weakness with zonesthesia on the chest and back for 2 months.

(A) Sagittal fluid attenuated inversion recovery (FLAIR) T1WI scan showing long T1 signal of lesions at the C_7–T_2 levels.

(B) Sagittal fast spin echo (FSE) T2WI showing homogenous long T2 signal of intramedullary lesions in C_7–$T_{2, 5–6, 9}$, and a swollen appearance of the lesioned tissue.

(C) Sagittal MRI showing patchy enhancement of the intramedullary lesions.

(D) Enhancement MRI of intramedullary lesions at the transverse T2 level in the white matter showing non-closed ring-like enhancement, namely, open-ring sign.

Pathological findings of patients with tumor-like inflammatory demyelinating disease in the spinal cord

Six patients were misdiagnosed as having intramedullary gliomas, and inflammatory demyelinating pseudotumor was pathologically confirmed after surgical resection in these patients. Postoperative pathological findings revealed demyelination, hematoxylin-eosin staining showed lymphocytic infiltration around the vessels with a sleeve-like appearance (Figure 3E), and a large number of monocytes/macrophages infiltrated the deteriorated myelin in the white matter (Figure 3F).

Treatment and follow-up of patients with tumor-like inflammatory demyelinating disease in the spinal cord

After a definitive diagnosis, 36 patients were given normal adrenal cortical hormone therapy and immunoglobulin therapy. Three months later, neurological function had partly recovered in all 36 patients.

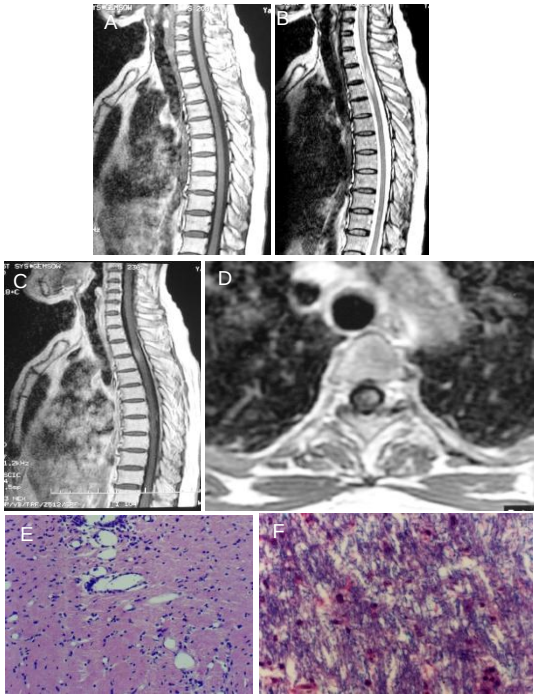

Figure 3 Imaging and pathological changes in a female 33-year-old patient with spinal cord tumor-like inflammatory demyelinating disease misdiagnosed as astrocytoma, who complained of lower extremity weakness for half a year.

(A) Sagittal fluid attenuated inversion recovery (FLAIR) T1WI scan showing long T2 signal of the lesion at the $T_{3–4}$ levels in the spinal cord.

(B) Sagittal fast spin echo (FSE) T2WI showing long T2 signal.

(C) Enhanced sagittal focal patchy enhancement.

(D) Enhanced transverse showed open-ring sign.

(E) By hematoxylin-eosin staining (× 300), inflammatory cell infiltration surrounded the lesion around the vein.

(F) Luxol fast blue staining revealed myelinated deterioration and obvious edema in lesioned tissue.

Lumbar puncture showed that the number of white blood cell was normal, but the protein level was increased in six patients, and immunoglobulin G (IgG) was increased in four patients. No new lesions were found by spinal MRI. The spinal cord was slightly atrophic and softening foci had formed, without enhancement in MRI. Visual-evoked potentials, brainstem auditory-evoked potentials and skull MRI findings were all normal. On electromyogram, nerve conduction velocity was still slowed and wave amplitude was decreased in one patient. F wave incidence was reduced in two patients. The other patients recovered completely. One patient who did not receive surgery presented with retrobulbar neuritis after

30 months. At 27 months after adrenal cortical hormone treatment, one patient who received surgery exhibited internuclear ophthalmoplegia and prolonged latency of P100. The patient was finally diagnosed as having multiple sclerosis. The period of follow-up lasted for 12–39 months. Multiple sclerosis was diagnosed according to the McDonald standard criteria revised in 2005[5].

DISCUSSION

Solitary space-occupying lesions on MRI may be inflammatory demyelinating pseudotumors

It is not clear what causes tumor-like inflammatory demyelinating disease, but it may be associated with viral infection, vaccination or the application of chemotherapeutic drugs, which could lead to vascular dysfunction[6-7]. However, there are still some investigators who think that it does not generally occur after infection or vaccination, despite a few rare cases. The results of our study suggest that most patients had an autoimmune disease or viral infection. From the perspective of immunology, the immune-mediated attack on myelin components is an important mechanism leading to myelin damage[8].

Clinical manifestations including sensory, motor and autonomic nerve damage

In the present study, young and middle-aged patients were prone to tumor-like inflammatory demyelinating disease, so age was not the main factor. A minority of patients had clear predisposing factors, most of which were associated with infection, while some showed special irritability such as agitation, trauma or psychentonia. Most cases had acute or sub-acute inflammatory demyelinating disease, clinically manifesting with spinal asymmetric, incomplete transverse lesions mainly in the lateral and posterior funiculi. The first symptoms were usually sensory disorders, followed by simultaneous sensory and motor disorders. Superficial sensory disorders are common and some were merged with deep sensory disorders. Moreover, the motor disorders behaved asymmetrically. These included monoplegia, paraplegia, quadriplegia and hemiplegia, and could be combined with peripheral nerve injury. Autonomic nerve damage is common in patients with urinary retention, urinary obstacles, and sweating dysfunction.

Spinal MRI examination is helpful for diagnosis

In the present study, focal lesions in the white matter of the spinal cord were observed, and these were most commonly seen in the lower cervical and upper thoracic cord. The lesions were solitary and space-occupying, and they had a clear boundary, being accompanied by edema in the peripheral area. On MRI, irregular long T1 and T2 signals were seen. Most lesions showed abnormal enhancement, usually with a ring-like enhancement of some part of the lesion. Non-closed ring-like enhancement (crescent or open-ring sign) on trans-axial scanning is of great pathognomonic value[9-11]. It is reported that the rate of such a symptom in the acute phase of demyelinating disease is up to 66%, but only 7% in non-demyelinating diseases (inflammation, tumor), and only 9% in typical multiple sclerosis[12]. The deterioration of foci generally occurs after 2 weeks to 5 months, with most of the deterioration occurring in the period 6–8 weeks[13]. However, in our study, the ratio of open-ring sign was less than 66%, showing that additional observations are needed. The worsening ring sign represents the boundary of demyelination. The degree of MRI aggrandizement was associated with the degree of macrophage infiltration. The edema surrounding the lesion would reduce or disappear during the course of diseases involving demyelinating, space-occupying lesions of the central nervous system, but gliomas would not show this kind of change. The internal part of the tumor might also show cystic degeneration but with rare bleeding or cavities. The inflammatory infiltration and edema usually disappear in the chronic inactive period. The focus of infection showed non-aggrandizement or partial one for enhanced scanning, and the spinal cord swelling could return to normal. The mechanism underlying the formation of the occupying lesion may involve an obvious inflammatory cell response of demyelinating plaques, while the edema around the plaque intensifies the lesion's space-occupying effect. However, lumbar puncture results exclude the involvement of other demyelinating diseases.

Mechanism underlying tissue edema and peripheral aggrandizement: inflammatory cells infiltrated around the lesion, especially around the peripheral area of small veins during the acute period, resulting in the destruction of the blood-brain barrier, which would lead to focal edema, and even to the emergence of hemorrhage and necrosis. On imaging, a low-density center and peripheral aggrandizement were observed; however, an inflammatory reaction could cause secondary lesions where microvascular thrombosis forms, resulting in tissue necrosis. Imaging revealed low signal intensity in the center. In addition, some chronic isolated lesions would repeatedly be aggrandized, which might be due to two factors: inflammatory infiltration caused by the continuous immune-mediated peripheral areas, or the destruction of the blood-brain barrier caused by demyelina-

tion. For the spinal space-occupying lesions with a longer period, the imaging manifestations revealed local swelling or atrophy in the spinal cord, and also local spinal atrophy for MRI follow-up. One patient had nerve dysfunction.

It is worth noting that spinal gliomas generally show obvious aggrandizement and a clear boundary. Therefore, it is difficult to distinguish these from demyelinating pseudotumor. However, gliomas are often located in the central area of the spinal cord and often occur in conjunction with syringomyelia, while demyelinating pseudotumors tend to be located in the white matter of the spinal cord, and no secondary cavity lies in its adjacent areas. Thus, demyelinating pseudotumors in the spinal cord show a number of the characteristics of tumors in terms of MRI manifestations, so they are often misdiagnosed as neoplastic lesions. Six of the 36 cases had local space-occupying lesions, without infection, accounting for 8% compared with intramedullary tumor in the same period.

Hormone experimental therapy benefits clinical diagnosis

The MRI manifestations of demyelinating lesions in the recovery period differ from those in the active period, and this difference could contribute to a clinical diagnosis of multiple sclerosis. When it is difficult to distinguish tumors from demyelinating lesions, especially in cases showing early onset, and also in patients with no obvious hormone contraindications, hormone experimental therapy with adequate dosage and treatment duration could be carried out. Intramedullary lesions can then be identified by comparing MRI performances before and after treatment, in combination with a consideration of clinical changes. In our present study, 36 patients improved markedly with shrunken foci after treatment. Glioma commonly shows a slow onset with mild clinical manifestations and slow development. Its imaging manifestations are worse than its clinical ones, possibly because early gliosis does not damage normal tissue. Hormone treatment has a poor effect on gliomas. Although symptoms caused by spinal tumors are temporarily relieved by hormone treatment, such relief does not last for a long time. MRI foci are not been significantly reduced; on the contrary, they may invade extramedullary lesions making the space-occupying effect more obvious, even blocking the canalis spinalis with time. Such lesions show homogeneous aggrandizement, and part of these tumors could appear necrotic, with liquefaction and cystic change. The clinical symptoms might also worsen[14].

Pathological characteristics indicative of immune damage

In the present study, the pathological process began with mononuclear cell infiltration, and then resulted in the destruction of the myelin sheath, after which sleeve-like lymphocytic infiltration appeared in the perivascular area. Vascular damage was also observed owing to secondary disease involving immune complexes and complements. This hypothesis considered that the complement causes endothelial injury, which was the earliest lesion, whereas perivascular demyelination and tissue destruction were only secondary changes. Vasculitis could be multifocal, but the white matter and its edges were not frequently affected.

Observation of two symptoms together may indicate the presence of demyelinating disease. One is lymphocyte-based inflammatory infiltration around the perivascular area, which has greater indicative significance when seen in young people, although this change could also be found in a handful of cases with glioma. The other symptom is the presence of massive macrophages within a white matter lesion, which reflects a non-tumorous lesion. This is the reaction of an organism to remove the scraps left following myelin destruction. The emergence of a large number of macrophages suggests non-neoplastic lesions, and this change never appears in untreated patients with glioma. However, macrophages displayed clear borders, the cytoblastoma was rich and stained granular in paraffin sections, and the cells were a consistent size. Sometimes, when macrophages are concentrated, oligodendroglioma may be misdiagnosed. Myelin staining could distinguish this condition from oligodendroglioma[15]. In addition, Luxol fast blue staining shows demyelination of different degrees and the remaining axon. In chronic cases, the number of macrophages is significantly decreased, while the number of glial fibers is increased or they form a scar, while fibrous astrocytes gradually replace stellate cells. The myelin debris phagocytosed by macrophages is degraded into neutral fat, so the cytoplasm appears foamy. It is difficult to identify blue-stained myelin debris using Luxol fast blue staining, but these features can be detected with Luxol fast blue. Active proliferation and nuclear hyperchromatism, and sometimes mitoses could be seen. Inflammatory infiltration of lymphocytes still appears in the perivascular area, but it is not as obvious as in acute lesions.

In this study, massive macrophages appeared within lesions and lymphocyte-based inflammatory infiltration was seen around the perivascular area in all six misdiagnosed cases. Luxol fast blue staining revealed that

the myelin was lost at the lesion site, and all six patients were shown to have tumor-like inflammatory demyelinating disease.

Possible damage to the gray matter and peripheral nervous system

In this study, some patients had decreased peripheral nerve conduction. They also showed few F waves. The extent of peripheral nerve damage is associated with several factors, such as functional defects, the course of lesion development and lesion location. The worse the neurological functional defect was, the longer was the course of disease, and the more obviously the amplitude of the wave decreased. Electromyography can thus be used to evaluate peripheral nerve damage, and so it has a certain practical value for judging prognosis. Demyelinating disease of the central nervous system could involve the peripheral nervous system and the gray matter. At the same time, recurrent Guillain-Barr Syndrome and chronic inflammatory demyelinating polyradiculoneuropathy also involve the central nervous system. These two diseases may have a common etiology and pathogenesis. There were two suggested causes of this phenomenon at present: (1) the peripheral nerve system and the central nervous system have the same antigenic components; and (2) genetic differences among individuals might lead to a variety of immune responses, which could result in damage to the nervous system in a variety of places. In this study, one patient scored 7 on the expanded disability status scale. Electromyography examination showed decreased wave amplitude. The viewpoints discussed above were supported. Cortical disease has emerged as a critical aspect of the pathogenesis of multiple sclerosis, being associated with disease progression and cognitive impairment in patients with early-stage multiple sclerosis. Cortical demyelinating lesions are inflammatory and strongly associated with meningeal inflammation[16]. Recent research into cerebral cortical demyelination and remyelination in appropriately processed postmortem multiple sclerosis tissues has provided innovative hypotheses regarding the pathogenesis of multiple sclerosis lesions, including the identification of targets for therapy in the early stages of the disease[17].

Differential diagnosis includes glioma and primary central nervous system lymphoma

Tumor-like inflammatory demyelinating disease in the spinal cord is very likely to be misdiagnosed as glioma because of its obvious space-occupying effect. Juveniles are more susceptible to spinal cord glioma, which would harm the cervical-thoracic cord, yet gliomas are located in the central area of the spinal cord, and commonly occur in parallel with syringomyelia. It often exhibits closed annular or homogeneous enhancement on enhanced scanning. Open-ring sign is rare. Imaging findings are generally more serious than those of clinical examinations. Poor outcomes following adrenal cortical hormone therapy can also be used to distinguish inflammatory demyelinating disease from glioma. It should be noted that hormones have an anti-inflammatory effect and relieve edema; that is to say, hormones can inhibit the peritumoral edema to some extent. However, the tumor will grow continuously and become aggravated, so the results of hormone therapy cannot be regarded as the main basis for excluding glioma. As the disease progresses, the occupying effect is more obvious, accompanied by syringomyelia. Tumor-like inflammatory demyelinating disease is generally located in the white matter around the spinal cord and has no secondary syringomyelia[18].

The reasons why six patients from this study were misdiagnosed lie in the lack of experience of clinicians, the lack of typical clinical manifestations, the lack of any apparent cause before onset, and the single phase course of disease, along with the slow progression in seriousness. Lesions remained unitary and space-occupying, involving the gray matter. No hormone therapy was implemented.

Primary central nervous system lymphoma often involves the deep gray matter, and shows a dramatic response to hormone therapy. It lacks the pathological features of demyelinating pseudotumor (*e.g.*, demyelination), although the axonal pathology remains. Tumorous lymphocytes infiltrate the perivascular area and the vascular wall. These tumorous lymphocytes can be atypical and undergo mitosis, and the proliferative cells are often type B lymphocytes with CD20 expression. However, it is the reactive or immune-mediated lymphocytes that infiltrate the peripheral area in cases of tumor-like demyelinating pseudotumor lesion, and they include both type B lymphocytes and type T lymphocytes. What is more, the tumor-like demyelinating pseudotumor lesion is a demyelinating disease of cell-mediated immunity, and the cells infiltrating the perivascular area are mainly type T lymphocytes, showing expression of CD43 and CD45RO. In brief, whenever intramedullary tumor of the spinal cord is diagnosed, it should be considered whether it is related to the identified problems of inflammatory demyelinating disease. With comprehensive inspection and serious data collection, some misdiagnoses may be avoided. Demyelinating pseudotumor is easily misdiag-

nosed as intramedullary tumor; therefore, we offer the following suggestions. (1) Consideration should be given to inflammatory demyelinating disease when the intramedullary lesions with a space-occupying effect appear clinically, and disease cases should be collected and analyzed in as much detail as possible. Then examinations such as lumbar puncture, immune, electrophysiological or neuroimaging examinations should follow. Meanwhile, adrenal cortical hormone therapy may be tried. (2) Spinal cord biopsy could be considered if the symptoms do not improve within the short term, and if the space-occupying effect persists[4]. Radiotherapy or operation should not be carried out blindly, as these have adverse consequences for patients. With the popularization and development of stereotactic technology, biopsy has become a simple and effective method with which to diagnose the qualities of suspicious lesions[19]. For some isolated space-occupying lesions, spinal cord biopsy is not only safe and accurate, but is also associated with little trauma. Therefore, it is worthy of clinical promotion and popularization.

Good prognosis after therapy

Conservative treatments represented predominantly by adrenal cortex hormone therapy should be carried out after diagnosis, accompanied by follow-up. Tumor-like inflammatory demyelinating disease in the spinal cord shows as a unique single lesion in most patients, and mostly has a single phase; in some it can develop into multiple sclerosis. Therefore, it is important to explore the distinctive and sensitive predictive factors for development of multiple sclerosis, and to seek an efficient and effective therapy with fewer side effects. In previous studies, most clinically isolated syndrome patients developed multiple sclerosis; moreover, the proportion of patients developing multiple sclerosis gradually increases with passing time[20-24]. In this study, two patients who converted to multiple sclerosis had only a short observation time; the proportion of patients developing multiple sclerosis would gradually increase with time. Related examinations, such as visual-evoked potentials and skull MRI, should be performed at follow-up. Some other related examinations should be carried out, such as brainstem auditory-evoked potentials and skull MRI. The clinically isolated syndrome that developed into multiple sclerosis can be predicted based on the following aspects. (1) It is associated with Lhermitte's syndrome, cramps, and zonesthesia. (2) MRI: The numbers of lesions are independent predictive markers, which develop into multiple sclerosis within a relatively short period of time[25]. These parameters can help to predict whether the syndrome will convert to multiple sclerosis. Therefore, they should be examined by MRI during the period of onset; furthermore, MRI examination should be implemented repeatedly during the follow-up period to observe dynamic changes in the lesions. One patient presented with internuclear ophthalmoplegia and was diagnosed as having multiple sclerosis after 27 months. The patient's symptoms were asymmetrical, with prominent sensory symptoms, reflecting the small lesion and edema to a lesser degree. All of these manifestations suggest that the syndrome can easily develop into multiple sclerosis; therefore, follow-up should be continued. At present, treatments for inflammatory demyelinating disease include some immunosuppressive agents such as corticosteroids, cyclosporin A, azathioprine, and cyclophosphamide[26]. Immunoglobulin can seal off pathogenic antibodies and T cell receptors, and suppress the immune response, so it can enhance non-specific immunity. The skull and spinal cord MRI examinations performed in this study found no new lesions during the period of follow-up. This may be related to the application of immunoglobulin. Interferon-β can reduce the clinically isolated syndrome recurrence rate by 30%, and can also delay its conversion to multiple sclerosis[27]. However, it is an expensive, seriously limiting clinical application. Although the effects of immunomodulators have been affirmed, this does not mean that they are effective. Prompt immunomodulator treatment works effectively in the early stage of multiple sclerosis, but, as the disease progresses, it may become less effective after degenerative changes.

It is generally believed that selective immunosuppression can be achieved by monoclonal antibody therapy. However, there is no clinical evidence supporting a specific monoclonal antibody therapy to date. Adhesion molecules play an important role in helping lymphocytes at the blood-brain barrier, and adhesion molecular therapy is also a promising immune therapy. Some clinical research on treatments for multiple sclerosis targeting adhesion molecules is underway. In addition, other inhibitory mediators of inflammation cytokines, such as interleukin-2, interleukin-10 and transforming growth factor R, also have therapeutic prospects. Among patients treated with plasma exchange for a steroid-refractory central nervous system inflammatory demyelinating disease, 59% exhibited moderate to marked functional neurological improvement within 6 months following treatment[28]. Recent studies demonstrate that using either mouse neural stem cells or human oligodendrocyte progenitor cells derived from human embryonic stem cells could promote remyelination in mice persistently infected with murine herpes virus[29]. The results of our study suggest

that through imaging and pathological examinations, demyelinating pseudotumor in the spinal cord has similarities to intramedullary tumor, and the open-loop syndrome has a higher specificity. Hormone therapy can be beneficial to make an effective diagnosis. It is necessary to collect more cases to explore and analyze the clinical features, and thereby reduce the rate of misdiagnosis.

In summary, tumor-like inflammatory demyelinating pseudotumor in the spinal cord is very easily misdiagnosed as intramedullary tumor because of its space-occupying effect[30]. Therefore, MRI contrast enhancement is needed to identify open-loop syndrome. Pathology varies, with myelin destruction but axonal retention. Luxol fast blue staining is of great value in the diagnosis. Adrenal cortex hormone therapy can be implemented; however, surgery should not be carried out blindly. The prognosis is good, although some cases convert to multiple sclerosis. The reason why a few patients develop multiple sclerosis is not at present clear, and autopsy is not performed in most cases. Further follow-up is needed.

SUBJECTS AND METHODS

Design

A retrospective observational study.

Time and setting

This study was performed in Yantai Shan Hospital, China, from June 1999 to March 2012.

Subjects

Patients with clinically diagnosed inflammatory demyelinating pseudotumor who received treatment in Yantai Shan Hospital, China from June 1999 to March 2012 were included in this study. They were residents of Yantai, Shandong Province, China, and had been living in the city for more than 10 years.

Inclusion criteria

(1) First attack by inflammatory demyelinating pseudotumor; aged 20–70 years; non-transverse myelopathy with limb weakness and numbness, which may be accompanied by urinary and bladder disorders.
(2) Physical examination: lesions of spinal cord but not cranial nerve and cerebral cortex.
(3) MRI examination: intramedullary lesions indicative of tumor-like inflammatory demyelinating disease.
(4) Normal brain MRI and brainstem auditory-evoked potential examinations.
(5) After conventional hormone treatment, no new symptoms and signs were observed during a 6-month follow-up period. The lesions shrunk as shown by MRI examination.
(6) Patients that were misdiagnosed as having tumors and definitively diagnosed by pathological examination after surgical resection.

Exclusion criteria

(1) Intramedullary and extramedullary tumor, metastasis, vascular disease, spinal cord tuberculoma, metabolic disorders, spinal cord injury, cervical vertebra disease and lumbar disc herniation.
(2) Combined with intracranial lesions, cranial nerve injury, and abnormal brainstem auditory-evoked potential.
(3) Acute transverse myelitis.

Clinical resources

Clinical resources included general information, past medical history, inducing factors, mode of onset, initial symptoms and clinical manifestations. After clinical definitive diagnosis, a judgment was performed by co-operation between three professional neurologists in terms of inspection, record and registration from the aspects of sensory, motor and autonomic nerve function.

Methods

Detection of immune system injury by lumbar puncture examination

Protein was quantitatively detected by original reagents and using the timing method with an automatic biochemistry analyzer UNICEL DXC 800 (Beckman Coulter Co., Ltd., Brea, CA, USA). Immunoglobulin was quantitatively detected using the immune turbidimetry method with a Behring BN ProSpec analyzer (Dade Behring, Deerfield, IL, USA).

Visual-evoked potentials: P100 latency exceeding 119 ms was considered to be extended latency.

Brainstem auditory-evoked potentials: Wave V amplitude decreased or disappeared (87%); III–V interpeak latency was prolonged (28%); III–V interpeak latency/I–V interpeak latency was greater than 1; wave III disappeared and I–V interpeak latency was prolonged[31].

EMG examination

Reverse stimulus: the median nerve and ulnar nerve in the upper limbs and the tibial nerve and peroneal nerve in the lower limbs were examined. Motor nerve conduction velocity, amplitude, EMG and F waves were examined. The motor nerve conduction velocity was con-

sidered slow when upper limb conduction velocity was lower than 50 m/s and lower limb was below 40 m/s.

The upper limb motor amplitude was considered reduced when it was lower than 4 mV and felt to be lower than 2 μV. The lower limb motor amplitude was lower than 4 mV and felt to be lower than 10 μV. Electromyography with fibrillation wave or positive sharp wave was regarded as abnormal and F wave rate less than 60% was abnormal.

MRI examination

A 1.5 T superconductive MRI scanner (Signa Advantage Horizon; GE Healthcare, Fairfield, CT, USA) was used. In routine scanning, head and spine surface coils were used. The scanning sequence and parameters were as follows: fluid attenuated inversion recovery (FLAIR T1WI; repetition time 2 045 ms; echo time 19.9 ms; inversion time 860 ms) and fast spin echo sequence (FSE T2WI; repetition time 2 000 ms, echo time 121 ms). Sagittal and axial scanning was performed. Enhanced contrast agent gadolinium-diethylenetriaminepentaacetic acid (Gd-DTPA) was injected by intravenous bolus at a dose of 0.1 mmol/kg. Three radiologists read the MRI images and made the definite diagnosis. The lesion region, shape, size, signal, peripheral edema, enhancement and accompanying signs were observed in plain and enhanced MRI images.

Pathological examination

Hematoxylin-eosin staining and Luxol fast blue staining were performed. The reagents used were purchased from Beijing Zhongshan Golden-Bridge Biotechnology Co., Ltd., China. An Olympus BX41 microscope was purchased from Shanghai Lai Electronic Technology Co., Ltd., China.

Treatments and follow-up

After diagnosis, 36 patients were treated by intravenous injection of 500 mL of 5% glucose containing 500–1 000 mg methylprednisolone, once a day, for 3–5 days. At the same time, 0.4 g/kg immunoglobulin was intravenously injected per day for 5 successive days. Then, prednisone produced by the Belgian Pharmacia Co., Rijksweg, Puurs, Belgium, was orally taken 1 mg/kg per day once every morning, with the dose reduced by 20% every week. Prednisone administration lasted for 3 months. The clinical manifestations, cerebrospinal fluid, visual-evoked potentials, brainstem auditory-evoked potentials (visual, auditory), skull and spinal MRI examination and records were assessed during the follow-up period.

Research background: Inflammatory demyelinating pseudotumor, which is easily confused with intramedullary neoplasms and finally pathologically diagnosed by surgical resection, is commonly encountered in the clinic.

Research frontiers: Inflammatory demyelinating pseudotumor shows a manifestation atypical of tumors in terms of clinical and imaging evaluations and is often misdiagnosed as intramedullary neoplasm. However, the non-closed rosette-like reinforcement (open-loop sign) surrounding the lesion site as shown by magnetic resonance imaging is helpful for clinical diagnosis.

Clinical significance: This paper summarizes the clinical and imaging properties of inflammatory demyelinating pseudotumor in the spinal cord, aiming to decrease the misdiagnosis rate in the clinic and improve patients' quality of life.

Academic terminology: Inflammatory demyelinating pseudotumor is named for its space-occupying phenomenon, similar to tumors. The crescent sign, *i.e.*, a non-closed structure with its opening towards the center in the white matter, is seen by enhancement on magnetic resonance scanning.

Peer review: The clinical and imaging properties of inflammatory demyelinating pseudotumor in the spinal cord provide novel objective evidence for clinical diagnosis and treatment of this disease, provide novel insights into diagnosis and differential diagnosis of this disease, and provide guidance for clinical practice.

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(Reviewed by Daniel M, Haase R, Lv J, Zhang RX)
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