ORIGINAL RESEARCH

Differentiation of Intraspinal Tuberculosis and Metastatic Cancer Using Magnetic Resonance Imaging

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Purpose: This study aimed to explore the differences in the magnetic resonance imaging (MRI) findings between intraspinal tuberculosis and metastatic cancer, which may aid in making the correct diagnosis.

Patients and Methods: The clinical features and MRI findings of 15 patients with intraspinal tuberculosis and 11 patients with intraspinal metastatic cancers were retrospectively analyzed.

Results: The mean ages of the patients with intraspinal tuberculosis and metastatic cancer were 26.3 (15–42) and 52.1 (38–67) years, respectively. All intraspinal tuberculosis cases were secondary to primary extraspinal tuberculosis, including tuberculous meningitis (11/15), as well as pulmonary (9/15), vertebral (5/15), urinary tract (1/15), abdominal (1/15), cervical lymph node (1/15), and multisystem tuberculosis (9/15). The intraspinal metastases originated from the breast (5/11), lung (3/11), kidney (1/11), ovarian (1/11), and nasopharyngeal cancers (1/11). Both intraspinal tuberculosis and metastatic cancers presented with multiple intra- and extramedullary lesions throughout all regional segments of the spinal canal, accompanied by irregularly thickened meninges. Intraspinal tuberculous lesions had indistinct edges that integrated with each other, most of them exhibiting obvious enhancement on MRI. Conversely, intraspinal metastatic lesions were distinctly separated with clear edges and exhibited lesser enhanced MRI than intraspinal tuberculosis.

Conclusion: A combined analysis of clinical features and MRI findings may be helpful in differentiating intraspinal tuberculosis from metastatic cancer.

Keywords: intraspinal tuberculosis, intraspinal metastatic cancer, intramedullary nodule, leptomeningitis

Introduction

Tuberculosis can involve all human organs. Although the lungs are most commonly involved, extrapulmonary tuberculosis accounted for 15% of all tuberculosis cases according to the WHO in 2016.[1,2] As a common type of extrapulmonary tuberculosis, intraspinal tuberculosis occurs increasingly, although its accurate incidence is unknown, which is in the same situation as intraspinal metastasis.[3] Both intraspinal tuberculosis and metastatic cancer may be rare, but they are difficult to differentiate because of their similar presentations and the high negative incidence of microbiological test for tuberculosis in cerebrospinal fluid (CSF) and their prognoses are completely different.[1,4] Most patients with intraspinal tuberculosis can achieve remarkable recovery after early diagnosis and treatment, whereas intraspinal metastatic cancers have a poor treatment response and poor prognosis.[5–7] To the best of our knowledge,

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although the optimal treatment of both diseases remains controversial, early accurate diagnosis can be helpful to improve neurological deficits and quality of life.[8–13]

Magnetic resonance imaging (MRI) is the modality of choice for the diagnosis of intraspinal lesions.[3,13] According to previous reports, intraspinal tuberculosis and metastatic cancer present differently in several aspects, including average patient age, distribution of the lesions, and clinical histories, but they also share the following features on MRI: significant spinal dural enhancement, intramedullary nodules, edema, space-occupying effect, meningitis, and hydrocephalus.[3] In this study, we aimed to explore the differences in the MRI findings between intraspinal tuberculosis and metastatic cancer, thereby facilitating their accurate diagnosis. We hypothesized that combined analysis of clinical and MRI features may be helpful to distinguish intraspinal tuberculosis from metastatic lesions of cancers.

Materials and Methods
Patients

A total of 26 inpatients, admitted in our hospital from November 2012 to May 2018, were retrospectively enrolled in this study, including 15 patients (8 men and 7 women) with intraspinal tuberculosis and 11 (5 men and 6 women) with intraspinal metastases. All these patients received multiple gadolinium contrast MRI examinations of the spine, which showed obvious subdural and intramedullary lesions; patients with epidural lesions were excluded. Their medical records, including clinical features and imaging findings, were reviewed and analyzed. This study was approved by the Ethical Committee of the First Affiliated Hospital of Chongqing Medical University (IRB ID: 2019-357). Waiver of consent was obtained given the observational nature of the project (retrospective archive study). We declare that the patient data confidentiality has been protected in the course of studying and the study has been conducted in accordance with the Helsinki Declaration.

MR Imaging

All the MRI examinations were performed on a 1.5 T GE Signa Excite MR image scanner (General Electric, Milwaukee, WI, USA). The MR imaging protocols included sagittal, coronal fast spin-echo (FSE) T2-weighted (repetition time [TR] = 3200 ms, echo time [TE] = 51 ms), and T1-weighted imaging (TR = 340 ms, TE = 10 ms) of the whole spine, with axial T2- and T1-weighted sequences for the interesting regions. The acquisition matrix was 256×256,

and the slice thickness was 3.5 mm with a 1.0-mm gap. Contrast-enhanced T1-weighted images were obtained from each patient after injecting the gadopentetate dimeglumine 0.1 mmol/Kg through the median cubital vein with the same scanning parameters.

Results
Patient Characteristics

All the 26 patients experienced progressive neurologic dysfunction of the lower extremities; weakness was the most common initial symptom, followed by pain, hypoesthesia with a sensory level, and eventually astasia. Some patients also experienced sphincter disturbance.

The mean age of the 15 patients with intraspinal tuberculosis was 26.3 (15–42) years. All these patients were negative for acid-fast smear microscopy and had no tuberculosis-specific findings in CSF analysis (including quantitation of lymphocytes, protein, and glucose). They were all secondary diseases, with primary lesions in extraspinal organs: the meninges (n = 11), lungs (n = 9), vertebrates (n = 5), urinary tract (n = 1), abdomen (n = 1), and cervical lymph nodes (n = 1); nine of them had multisystem lesions. Diagnosis of intraspinal tuberculosis was made based on the treatment response and radiographic changes following anti-tuberculosis therapy, as there were no specific clinical symptoms for intraspinal tuberculosis. According to initial manifestations, these intraspinal tuberculosis cases can be classified into two groups: (1) paraparesis (7 patients) and (2) tuberculosis symptoms (8 patients). The seven paraparesis patients were admitted for acute onset of lower back pain and lower extremity weakness (2 patients displaying coincident headache, dysphoria, and disturbance of consciousness); however, their diseases progressed rapidly and showed tuberculosis-related symptoms soon after admission. The eight cases with tuberculosis symptoms as the initial presentations displayed initial tuberculosis symptoms in other organs than the spine; the interval between symptom onset and development of intraspinal disease was <1 year. All the 15 patients with intraspinal tuberculosis achieved partial or complete recovery after anti-tuberculosis therapy; however, three patients eventually died within 2 months because of severe complications.

The mean age of the 11 cancer patients with intraspinal metastasis was 52.1 (38–67) years. All these patients experienced lower extremity weakness and pain within 2 to 19 years after being diagnosed with the primary cancers, which involved the breast (n = 5), lungs (n = 3), ovaries (n = 1), kidneys (n = 1), and nasopharynx (n = 1). All patients

had distant metastases in other organs prior to intraspinal metastasis, with brain metastasis being most frequently observed (n = 5), followed by chest wall metastasis (n = 1) and multiple metastases (n = 1). The 11 cancer patients with intraspinal metastasis experienced a rapid worsening of disease after the intraspinal metastasis was diagnosed and died within 4 years after the onset of the initial neurologic deficits due to poor treatment response.

Lesion Locations

Both intraspinal tuberculosis and metastatic lesions were observed throughout the entire spinal canal and most of them involved the subdural extramedullary region (Figures 1–4). However, their predisposed sites were different. Intraspinal tuberculosis mainly affected the thoracic (5/15), lumbar and sacral (5/15) regions, with the remaining 5 cases involving more than two regions of the spinal cord. For intraspinal metastases, no obvious location predilection was seen, with each of thoracic and lumbar lesions accounting for 1 of 11 cases, respectively, and the remaining 9 cases affecting more than 2 regions (one case involving the entire spinal cord).

MRI Findings

Multiple intraspinal nodular lesions together with irregularly thickened meninges on MR imaging were observed in both intraspinal tuberculosis and metastatic cancer patients. All intraspinal tuberculosis cases were additionally accompanied by leptomeningitis, which showed isointense on T1-weighted images and mixed iso- or slightly hyperintense on T2-weighted images, and obvious homogeneous linear, mottled, or patchy enhancement in more than two segments on enhanced T1-weighted images (Figure 1). The lesions had indistinct edges and appeared to integrate with each other, most showing obvious enhancement along with focal or diffuse spinal cord edema and syringomyelia (n = 6) (Figures 1 and 2). Other relevant MRI findings in intraspinal tuberculosis were as follows: adhesions and stenosis of the subarachnoid space (n = 3), enhancing thickened nerve roots (n = 4), and clearly defined intramedullary tuberculomas (n = 2). Tuberculomas were isointense on T1- and iso- or slightly hyperintense on T2-weighted images with homogeneous or ring enhancement (Figure 2).

The MRI findings of intraspinal metastatic cancer were similar to tuberculosis, but metastatic lesions were clearly separated from each other and exhibited lesser enhancement on MRI than intraspinal tuberculosis. Moreover, meningeal thickening caused by metastatic cancer was thinner and most frequently limited to four consecutive vertebral segments (Figures 3 and 4). Intramedullary nodules surrounded by focal edema (isointense on T1- and slightly hyperintense on T2-weighted images) together with a poorly defined border were observed in eight patients with intraspinal metastasis (Figure 3). Two metastatic patients presented multiple patchy areas of enhancing thickened meninges accompanied by the enhancing nodules.

Discussion

It could be difficult to differentiate intraspinal tuberculosis from metastatic lesions of cancer or other space-occupying lesions by relying solely on clinical symptoms and CSF analysis, as demonstrated in this study. However, these pathologies should be highly suspected when a patient with a current or previous history of tuberculosis or cancer presents with rapidly progressive neurologic deficits. Joint consideration of a patient's clinical features and MRI findings may be helpful to arrive at a correct early diagnosis and allow expedient appropriate treatment.

Intraspinal Tuberculosis

The worldwide incidence of intraspinal tuberculosis has been recently increasing.[3,6,14,15] Although a male predominance was reported, intraspinal tuberculosis predominantly occurs in younger patients of both genders, with a mortality of 20% in children aged <5 years and 60% in patients aged >50 years.[3,7,16–18]

Most intraspinal tuberculosis cases arise from a primary extraspinal source, with the lungs and intracranial region being the most common primary sites, as demonstrated in this study; these two primary tuberculous diseases disseminate to the intraspinal region through the blood and CSF, respectively.[19] But the primary intraspinal tuberculosis lesion was reported to be the most common original source in one study.[17] The thoracic segments were most commonly involved in our series. This involvement pattern can be attributed to the distribution of blood supply to the spinal cord: the thoracic segment receives nearly 45% of the spinal cord blood supply.[8,9]

Tuberculous leptomeningitis with intraspinal nodules was thought to be the most common feature of patients with intraspinal tuberculosis.[15–17] In the present study, enhanced T1-weighted images delineated the thickened meninges better and was more sensitive to detect tiny lesions compared with unenhanced images, while Gupta et al found no enhancement of leptomeningitis in a few patients, inferring that the contrast MRI imaging might have no benefit for differentiating
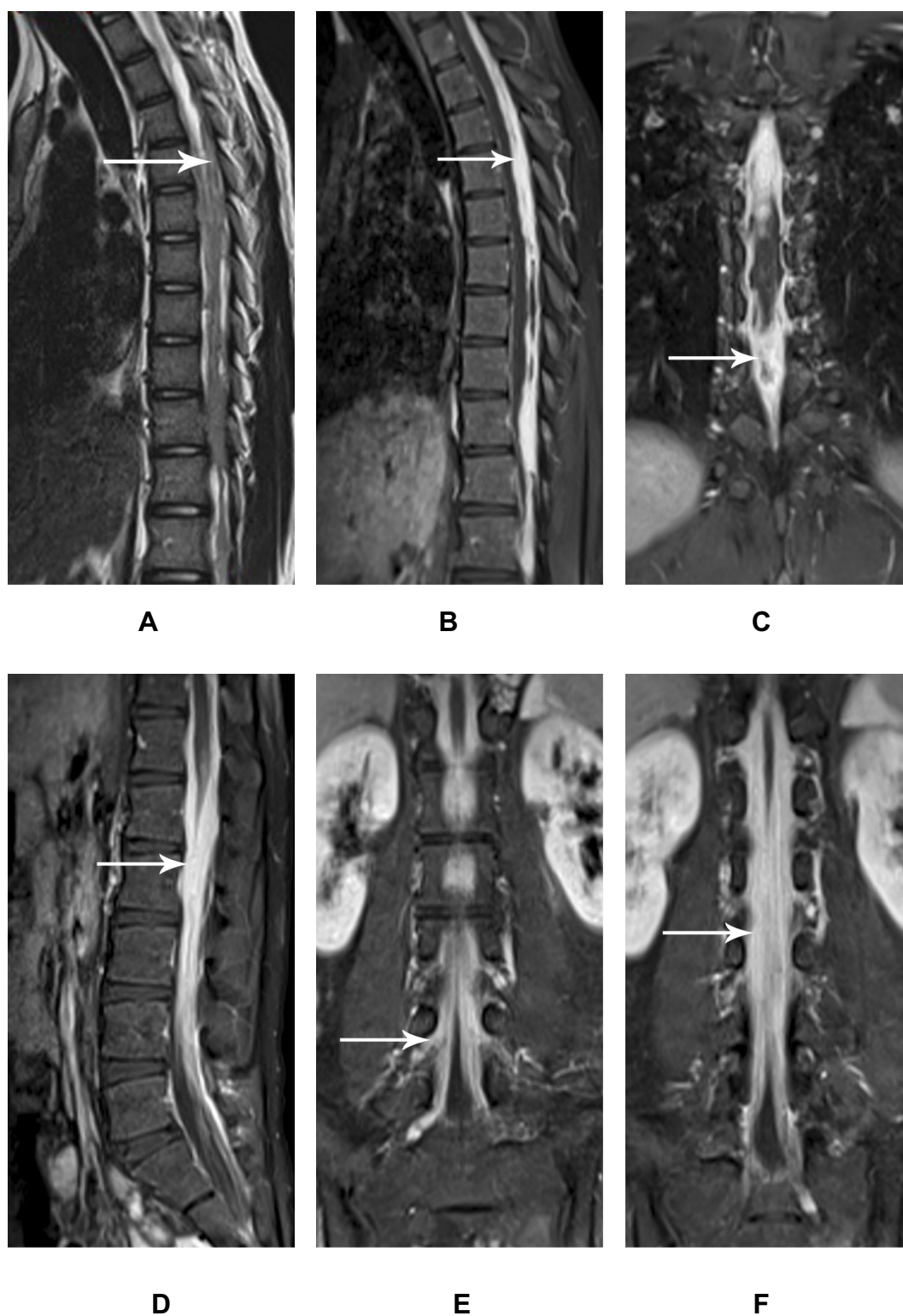
A　　　　　　**B**　　　　　　**C**

D　　　　　　**E**　　　　　　**F**

Figure 1 The irregularly thickened meninges of intraspinal tuberculosis show obvious homogeneous enhancement on MR images.
Notes: Intraspinal tuberculosis in a 21-year-old male. Sagittal T2WI (**A**) shows a slight hyperintensity of the irregularly thickened meninges (white arrow) and edema of the involved spinal cord. Gadolinium contrast MR images (**B–F**) show obvious enhancement of irregularly thickened meninges in the thoracic and lumbar segments (white arrow) that integrate with each other. Nerve roots are thickened with obvious enhancement bilaterally (**E**, white arrow).
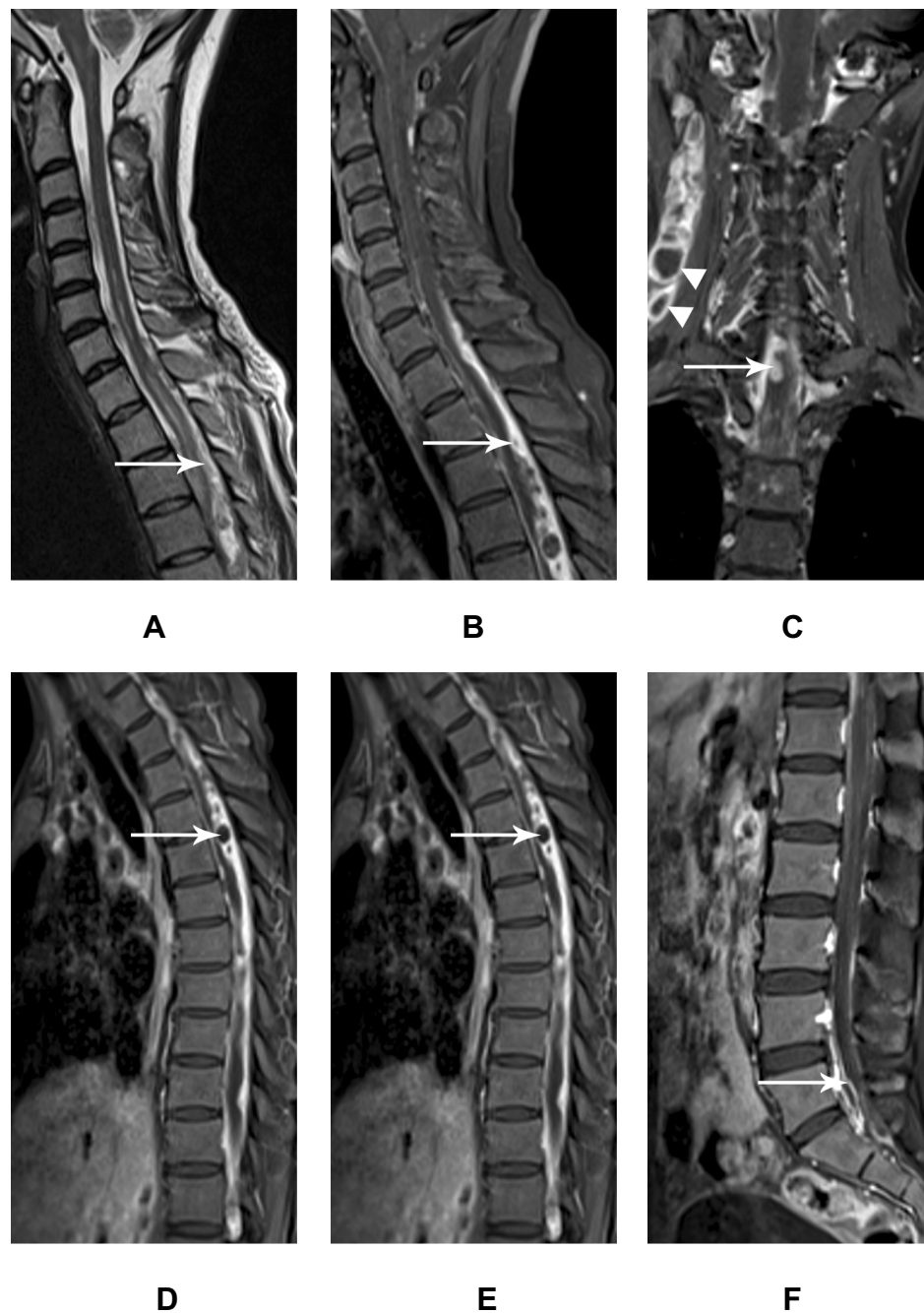**Abbreviations:** T2WI, T2-weighted imaging; MR, magnetic resonance.

Figure 2 Multiple intraspinal tuberculomas companied with thickened meninges in the cervical, thoracic, and lumbar segment.
Notes: Intraspinal extramedullary tuberculomas in a 25–year–old female. Sagittal T2WI (**A, D**) shows a slight hyperintensity of the tuberculomas (white arrow) and diffuse edema of the spinal cord. Gadolinium contrast MR images (**B–C, E–F**) show tuberculomas with both homogeneous (**C**, white arrow) and ring (**E**, white arrow) enhancement that integrate with adjacent irregularly thickened meninges. Cervical lymph nodes are enlarged and exhibit ring enhanced (**C**, white arrowhead).
Abbreviations: T2WI, T2-weighted imaging; MR, magnetic resonance.

tuberculous leptomeningitis from metastatic lesions of cancer, which was totally contrary to our findings.[17] The reason for this discrepancy was not clear and may be due to the different scanning protocols, contrast mediums, and different selection criteria for the enrolled patients. Other findings in patients with tuberculous leptomeningitis included hydrocephalus, intramedullary tuberculoma, spinal arachnoiditis, en plaque appearance of the sacral nerve roots, focal or diffuse edema in the spinal cord, and syringomyelia, which have also been reported by others.[3,16,20–23]

In this study, intramedullary tuberculous lesions were less common relative to extramedullary ones. As a specific form of
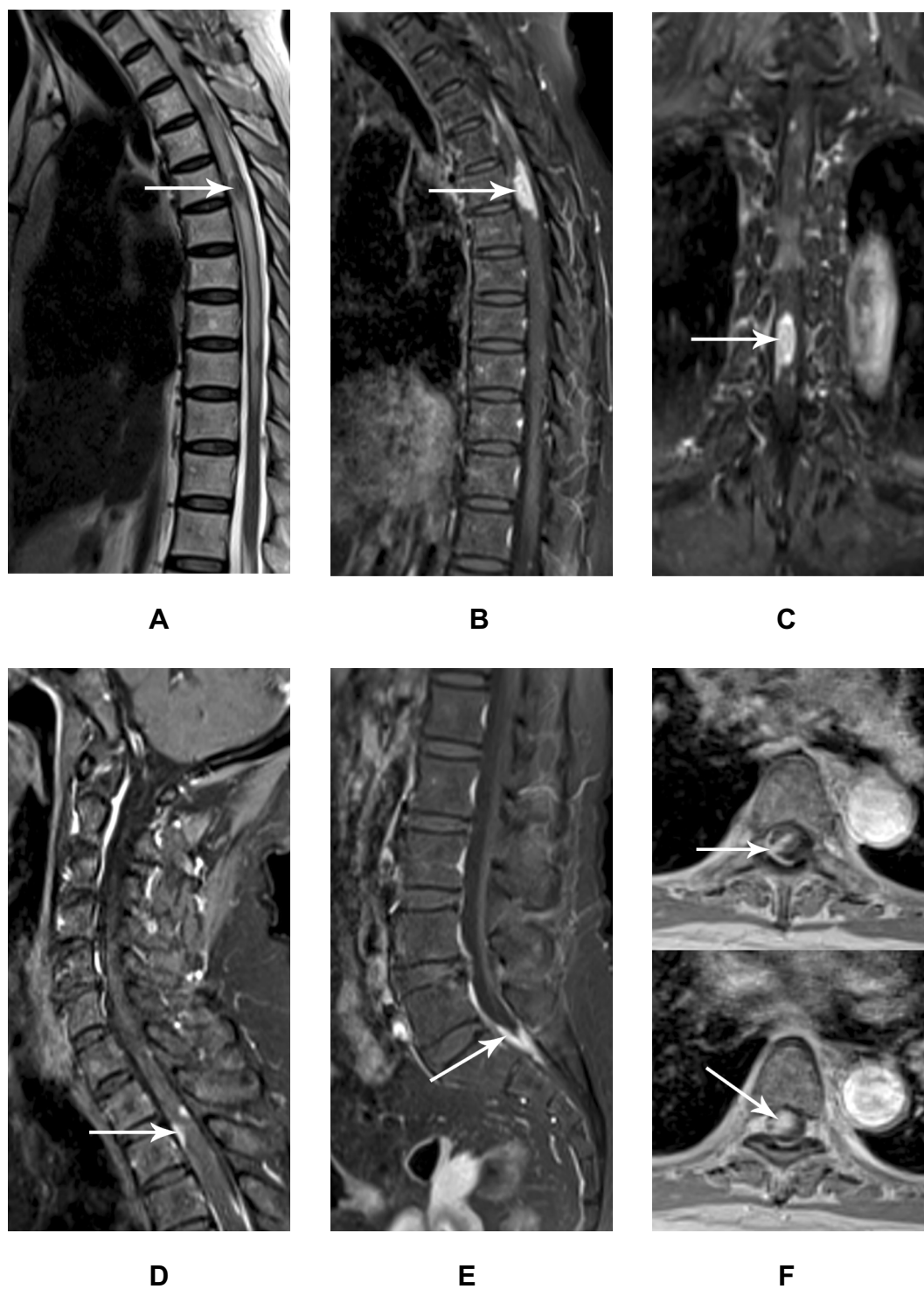
Figure 3 Multiple intraspinal metastatic lesions accompanied with slightly irregularly thickened meninges.
Notes: Intraspinal metastases in a 60–year–old female with breast cancer. Sagittal T2WI (**A**) shows slightly hyperintense intramedullary nodularities in the thoracic region (white arrow) accompanied by edema in the adjacent spinal cord. Gadolinium contrast MR images (**B**–F) show multiple intraspinal subdural lesions which are closely adherent to the slightly thickened meninges (white arrow).
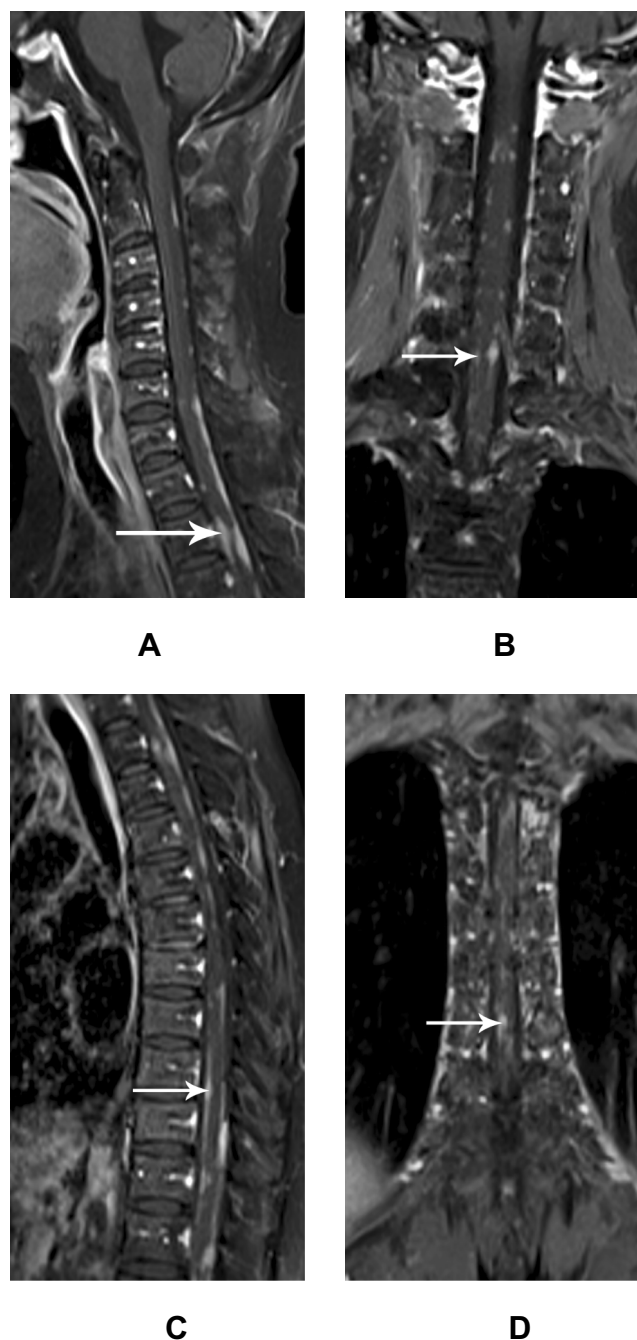**Abbreviations:** T2WI, T2-weighted imaging; MR, magnetic resonance.

Figure 4 Multiple intraspinal metastatic lesions accompanied by patchy thickened meninges.
Notes: Intraspinal metastases in a 64–year–old female with breast cancer. Gadolinium contrast MR images (**A–D**) show obviously enhanced nodules closely adherent to the slightly thickened meninges; the lesions have sharp margins and clear distinction between them (white arrow).
Abbreviations: T2WI, T2-weighted imaging; MR, magnetic resonance.

intramedullary tuberculous lesions, which may be mistaken for tumor, tuberculoma appeared a regular shape of isointense on T1- and slightly hyperintense on T2-weighted images, with homogeneous nodular enhancement seen in the early stage, while ring enhancement observed in the late stage, presumably

due to caseous necrosis in the lesion center. However, tuberculomas were more frequently detected in other studies that had similar imaging presentations to ours.[8,17,24] In the present study, we also found a 13% incidence of tuberculoma combined with leptomeningitis, which was similar to the 9.8% incidence, reported in a study of 122 patients.[25] All thickened meninges accompanied with nodules had undefined edges and seemed to be fused together, most of them showing enhancement on MRI; when involved, the cauda equina exhibited an en plaque appearance, and the nerve roots exhibited a thickening appearance.[16,26]

Intraspinal Metastasis of Cancer

The exact incidence of intraspinal metastasis of cancer is unclear, but the incidence of intramedullary spinal cord metastasis has been reported to be 0.9–2.1%.[11] Although the lungs are the most common sites of primary cancer, the breast ranked first in the frequency of occurrence locations for primary cancer in this study, which may be due to the small sample size.[5,11,12] As for pathologic mechanisms for intraspinal metastasis, three probable mechanisms have been suggested: (1) hematogenous spread via arteries and/or the vertebral venous plexus (Batson's venous plexus), (2) infiltration along with involved nerve roots, and (3) direct infiltration through the CSF.[11] Hematogenous spread is generally believed to be responsible for most cases. With regard to the involved regional areas of intraspinal metastasis, one study found that the cervical cord or the conus medullaris was most commonly affected (62%).[12] However, no obvious regional predominance was found in our study, which is consistent with the conception of most investigators that there is no regional segmental predilection for intraspinal metastasis. Furthermore, the involvement of the entire spinal cord was observed in most patients in our study.

Concomitant systemic metastases are often present in patients with intraspinal metastasis at the time of diagnosis, but some may be diagnosed without a definite primary cancer.[12] In this study, a known primary cancer had been determined for all patients before the diagnosis of intraspinal metastasis was made; meanwhile, brain metastasis was demonstrated to be the most common concomitant metastasis.

The MRI findings of intraspinal metastasis were similar to those of intraspinal tuberculosis, but some differences were remarkable. For patients with metastatic disease, a greater number of intramedullary nodules (solitary and/or multiple) surrounded by less edema were observed which appeared isointense on T1- and slightly hyperintense on T2-weighted

images. When menameninges were involved, linear enhancement can be observed, and when the cauda equina involved, thickening of the nerve roots observed. Extramedullary lesions appeared as thickened meninges, similar to those of intraspinal tuberculosis, but had sharp margins, limited scope, and evident distinction between lesions.

The MR spectroscopy was reported to apply in the differentiation of intraspinal nodules by a few studies. Lipid peak was thought to be radiological biomarker of tuberculoma while evaluated choline peak was thought to be specific for the metastasis, but the result was affected by many factors such as strong susceptibility artifacts and small size of intramedullary nodule for single-voxel placement, and it is not straightforward for the application of MR spectroscopy in intraspinal lesions, so the differentiation of intraspinal lesions may mainly rely on the MRI findings.[27,28]

Limitations

There were certain limitations to this study. Given its small sample size, it was difficult to extrapolate the results to a large population. In addition, the definite pathological diagnosis of the intraspinal lesions was not obtained; diagnosis of intraspinal tuberculosis was made based on the response to antituberculous therapy and intraspinal metastasis was diagnosed based on patient history of cancer and MRI findings. The validity of the study was also somewhat limited due to the lack of quantitative measurement and analysis regarding the imaging findings. We plan to enlarge the sample size and include quantitative measurements and analysis (such as MR spectroscopy, diffusion-weighted imaging) in a future study.

Conclusion

It is imperative to differentiate intraspinal tuberculosis from intraspinal metastasis of cancer due to their completely different prognosis, and combined consideration of a patient's clinical features and MRI findings can be helpful for their antidiastole. Intraspinal tuberculosis lesions may exist more obvious enhancement on MRI compared with intraspinal metastatic lesions and the meninges will become thicker when involved. Intraspinal metastatic lesions may have sharp margins, with evident distinction between each other, while tuberculosis lesions may appear to be fused and integrated with each other.

Acknowledgments

Disclosure

The author reports no conflicts of interest in this work.

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