Metastatic bone lesion due to methotrexate and etanercept 24 years after breast cancer treatment

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SUMMARY

A 72-year-old woman with rheumatoid arthritis presented with lumbar vertebral bone metastasis 24 years after mastectomy and radiotherapy for breast cancer. She was treated with prednisolone and methotrexate (MTX) for 11 months to which 10 mg of etanercept twice a week was added for a further 8 months. On the basis of this result, the possibility of a metastatic bone lesion appearing many years after cancer treatment should be considered when planning MTX and etanercept therapy.

BACKGROUND

The benefits of antitumour necrosis factor- α antagonists in rheumatoid arthritis (RA) as monotherapy and in combination with traditional disease-modifying antirheumatic drugs (DMARD) such as methotrexate (MTX) have been shown. However, the possible increased long-term risk of malignancy with these drugs was not determined.

CASE PRESENTATION

A 72-year-old woman had bilateral lower extremity pain and numbness radiating from the buttocks for 2 months. Two years ago, the patient showed symptoms of left finger numbness and stiffness. Although the joint findings and radiographs were atypical, the increase in the C reactive protein (CRP), erythrocyte sedimentation rate, rheumatoid factor and anticyclic citrullinated peptide antibody suggested RA. The fact that discontinuation of bucillamine worsened arthralgia also suggested RA. She was diagnosed with RA and treated with prednisolone at 10 mg/day and MTX at 6 mg/week for 11 months to which 10 mg of etanercept twice a week was added for a further 8 months. As she suddenly showed symptoms of lumbago, I was not able to investigate the possibility of vertebral metastasis soon. MRI showed a compression fracture of the L1 vertebra and a posterior tumour lesion on the L5 vertebra. Although I could not determine whether the lesion was benign or malignant on the L1 lesion, I suspected that the L5 lesion was metastasis.

INVESTIGATIONS

At our outpatient clinic, the patient's white cell count was $7500/\text{mm}^3$ and serum CRP level was 1.02 mg/dL. Liver and renal functions and electrolyte analyses were normal. The serum level of matrix metalloproteinase-3 (MMP-3) was increased to 219 ng/mL. MRI showed a compression fracture of the first lumbar (L) vertebra and a posterior tumour lesion on the L5 vertebra. There were two vertebral destructive lesions. One lesion was a

compression fracture of the L1 vertebra, and the other was a retropulsion tumour of the L5 vertebra. The former should be differentiated from a benign compression fracture. The L1 lesion showed a low-signal intensity within the vertebral body and upper and lower intervertebral discs on sagittal T1-weighted imaging (T1WI) (figure 1) and a conglomerated density on sagittal T2WI (figure 2). As the endplates of the vertebra were maintained, I could not determine whether the lesion was benign or malignant. On the other hand, the L5 lesion should be differentiated from infectious spondylitis. The upper and lower disc spaces of L5 were intact without a water-equivalent signal intensity on T2WI. The lesion was also composed of conglomerated low-density and high-density tumours with retropulsion of the posterior vertebral margin. Therefore, I diagnosed the L5 lesion as metastasis. The resected bone lesion specimen showed malignant cells which had a small high nuclear cytoplasmic ratio (N/C ratio) and formed a fine palisade-like structure and proliferated including muscle and fat cells (figure 3). Immunostaining was positive for CK7, CK20 and E-cadherin and negative for 34 β E12. Immunoreactivity for oestrogen

Figure 1 Sagittal T1-weighted imaging of the vertebrae.

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Figure 2 T2-weighted imaging of the vertebrae.

and progesterone receptors was 100% positive and Her2 was negative. Therefore, I diagnosed the patient with vertebral metastasis from breast cancer.

DIFFERENTIAL DIAGNOSIS

MRI showed a compression fracture of the L1 vertebra and a posterior tumour lesion on the L5 vertebra. Although I could not determine whether the lesion was benign or malignant on the L1 lesion, I diagnosed the L5 lesion as metastasis, which was also composed of conglomerated low-density and high-density tumours with retropulsion of the posterior vertebral margin. Vertebral tumours are classified into primary and metastatic tumours. Primary vertebral tumours are composed of various

Figure 3 The specimen of the metastatic bone.

disorders and occur in all age groups, but are very rare. On the other hand, metastatic vertebral tumours occur often in the middle and old aged groups. Lung, breast, prostate, gastric, thyroid and renal cancer are highly frequent in primary tumour. The patient had undergone a right mastectomy and radiotherapy for breast cancer 24 years earlier. I suspected metastatic bone tumour from breast cancer, despite the long time that had passed since her mastectomy. The resected bone lesion specimen showed malignant cells and immunostaining was positive for CK7, CK20 and E-cadherin and immunoreactivity for oestrogen and progesterone receptors was 100% positive. Therefore, I diagnosed it as metastatic vertebra from breast cancer.

TREATMENT

The patient underwent a laminectomy of the L1 vertebra and posterior fixation from the 11th thoracic to the L2 vertebra. Radiotherapy of the L1 and L5 vertebrae was also performed. Etanercept was stopped, but prednisolone and MTX were continued. The patient was then treated with selective third generation aromatase inhibitors.

OUTCOME AND FOLLOW-UP

The patient has remained in a stable condition after treatment.

DISCUSSION

The efficacy of tumour necrosis factor inhibition (TNFi) has been shown in numerous trials in patients with either early or established RA.¹ However, the risk of solid and haematopoietic malignancies with TNFi is much less clear, with meta-analyses of clinical trial data reporting conflicting results. Recently, Mariette *et al*² carried out a comprehensive literature search of MEDLINE, EMBASE, the Cochrane Database of Systemic Reviews, and American College of Rheumatology, European League against Rheumatism and British Society for Rheumatology conference abstracts that showed TNFi treatments do not increase the risk of malignancy, particularly lymphoma. They also stated that while it may be recommended that patients with a previous malignancy should not be treated with TNFi, data from two separate sources showed no significant increase in risk compared with similar patients treated with DMARD, the upper 95% CI including clinically meaningful increased risks (1.43³ and 2.17⁴)

Marsden *et al*⁵ reported that disseminated tumour cells in the bone marrow may exist in a dormant state for extended periods of time, and maintain the ability to proliferate on activation, engraft at new sites and form detectable metastases. On the basis of this result, the possibility of a metastatic bone lesion appearing many years after cancer treatment should be considered when planning MTX and etanercept therapy.

Learning points

- ▶ The disseminated breast cancer cells in the bone marrow may exist and regrow by using immunosuppressants.
- ▶ Although diagnostic difficulty exists when diagnosing a metastasis or infectious spondylitis or osteoporosis, MRI is very useful to differentiate them.
- ▶ The possibility of a metastatic bone lesion appearing many years after cancer treatment should be considered when planning methotrexate and etanercept therapy.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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