CASE REPORT

METASTATIC ADENOCARCINOMA IN A PATIENT WITH RHEUMATOID ARTHRITIS AFTER ANTI-TUMOR NECROSIS FACTOR α THERAPY

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The relationship between the anti-tumor necrosis factor alpha (anti-TNF α) agents and malignancies remains unresolved. A 65 year-old female was diagnosed with rheumatoid arthritis for 8 years. She received anti-TNF α therapy with a course of 24 vials since Sep. 2003. No significant side effects including serious infection were found during the first course of treatment. She started to receive a second course of Enbrel from 2005. Unfortunately, right hip pain developed in Aug. 2005 despite the treatment. Osteolytic lesions over acetabulum and ischium area were found by x ray. Abdominal CT scan showed multiple osteolytic changes over bilateral pelvic bones. Chest CT scan revealed segmental atelectasis in right upper lung. Right hip bone biopsy revealed metastatic adenocarcinoma. Positron emission tomography showed increased uptake in right upper lung. The relationship between the anti-TNF α agents and malignancies will be discussed.

Keywords: **rheumatoid arthritis, metastatic adenocarcinoma, anti-tumor necrosis factor alpha**

Rheumatoid arthritis can cause irreversible joint deformities and functional impairment. Greater understanding of the underlying mechanisms has revolutionized treatment and facilitated the development of new drug. The development of anti-tumor necrosis factor alpha (anti-TNF α) therapy has made a dramatic improvement in the treatment of RA [1]. The TNF α antagonists have been licensed for the treatment of rheumatoid arthritis, with over 70,000 patients now treated [2].

However, the use of these agents is accompanied by some worry about their long-term safety. The TNF was named because it was thought to have anti-tumor properties. Therefore it seems reasonable to investigate whether blocking the action of TNF might lead to an increased risk of

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malignancy [3]. Phase III trials tend to be short and exclude patients at high risk of cancer, not suited to detect and evaluate cancer as an adverse event; therefore, clinical monitoring after marketing is necessary [4].

The US Food and Drug Administration (FDA) reviewed the safety data on TNF antagonists about the risk of malignancy, and found that the numbers of tumor occurring was not sufficient enough to suggest a major increase in risk with short-term use, though the long-term risk remains to be investigated [5].

Herein we report a case of rheumatoid arthritis that developed metastatic adenocarcinoma following anti-TNF α treatment.

CASE REPORT

A 65 year-old woman was diagnosed with rheumatoid arthritis for around 8 years. She was quite well before except being admitted for a cholocystectomy due to chronic cholecystitis with cholelithiasis in Aug. 1995. She was diagnosed with rheumatoid arthritis in 1998 after having morning stiffness for more than 1 hour, symmetric involvement, hand arthritis and positive rheumatoid factor. Both 5 mg prednisolone and 500 mg salazopyrizen twice a day were the major treatment at that time, but she didn't follow up regularly. Then she went to our rheumatology department for further care in 2002; 200mg hydroxychloroquine twice a day and 7.5 mg methotrexate once a week, were the major disease modifying anti-rheumatic drugs. The Disease Activity Score (DAS) 28 score first evaluated in Feb. 2003 was 7.4, the ESR was 98 mm/hr, the numbers of tender joints were 15 and the numbers of swollen joints were 11, and the general health assessment was 95. At the second assessment, DAS 28 was 7.4, the ESR was 100 mm/hr, the numbers of tender joints were 12 and the numbers of swollen joints were 12, and the general health assessment was 90. No contraindications of using (Enbrel) such as active infection, chronic infection or old TB were noted before treatment. No other symptoms or signs of malignancy such as abnormal body weight loss or unexplained fever or mass were noted.

She received 24 vials of Enbrel from Sep. 2003 to Dec. 2003. The DAS 28 score was 4.3 after using Enbrel, ESR low down to 40 mm/hr. No significant side effects or serious infection were found during this course of treatment. Since Aug. 16, 2005, she started to receive Enbrel again after approval of preview; the DAS 28 score before using Enbrel was 7.14 in Mar. 2005 and 7.74 in Jul. 2005. No signifi-

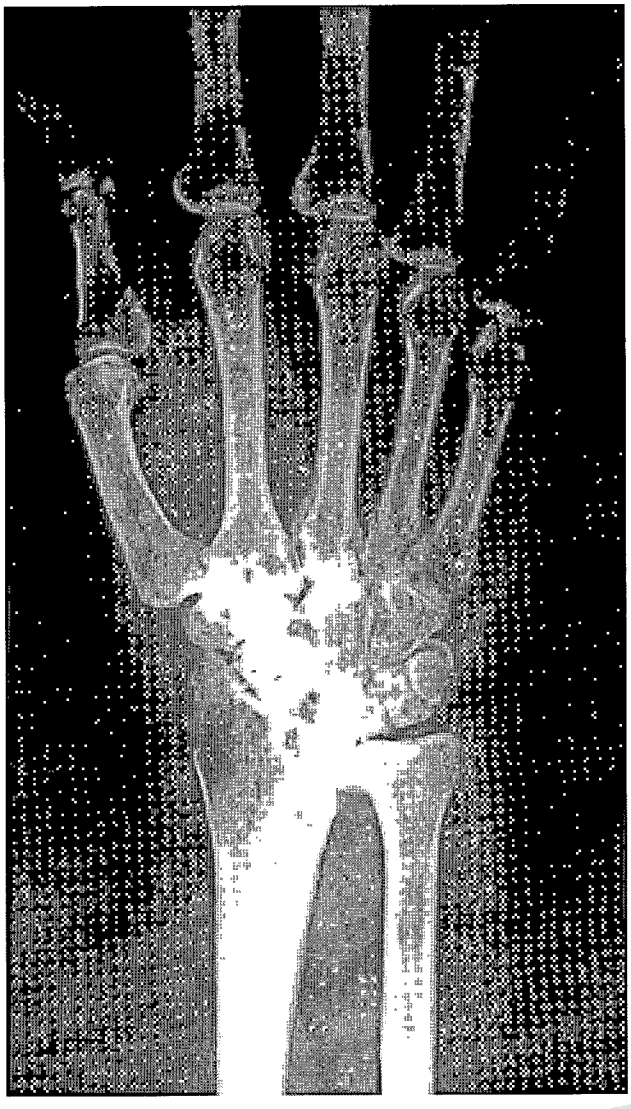

Fig.1 Right wrist films showed intercarpal, radiocarpal joint space narrowing and subchondral cyst formation.

cant side effects were found after initiating this course of treatment. Unfortunately, after 14 vials of Enbrel in this course of treatment, right hip pain was aggravated in Aug. 2005 despite aggressive treatment. Physical examination showed an obese woman, with stable vital signs. Swelling of multiple joints, including bilateral knee, elbow and wrist joints were noted. X-ray films of right wrist showed intercarpal, radiocarpal joint space narrowing and subchondral cyst formation (Fig. 1). After careful examination, multiple osteolytic lesions over bilateral pelvic bones were found on X-ray films (Fig. 2). Bone biopsy of right hip showed metastatic adenocarcinoma.

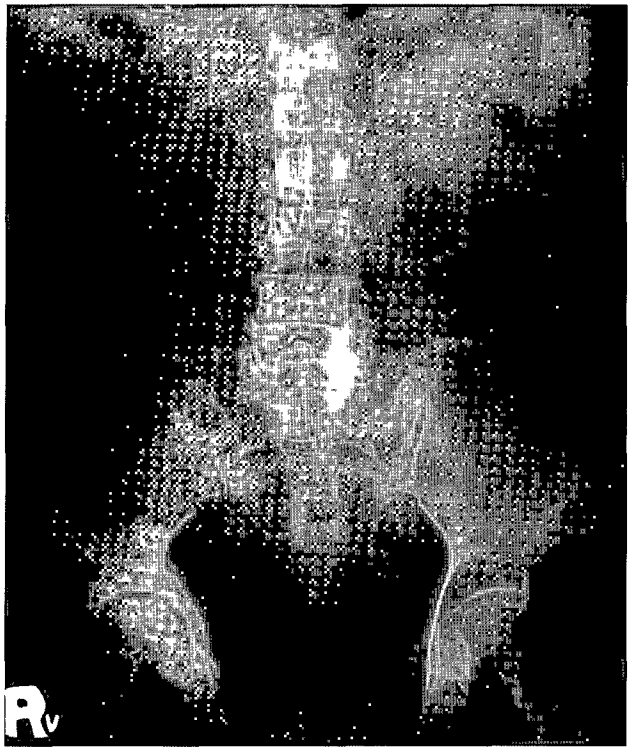

Fig. 2 Multiple osteolytic changes over pelvic bone and proximal femoral bones

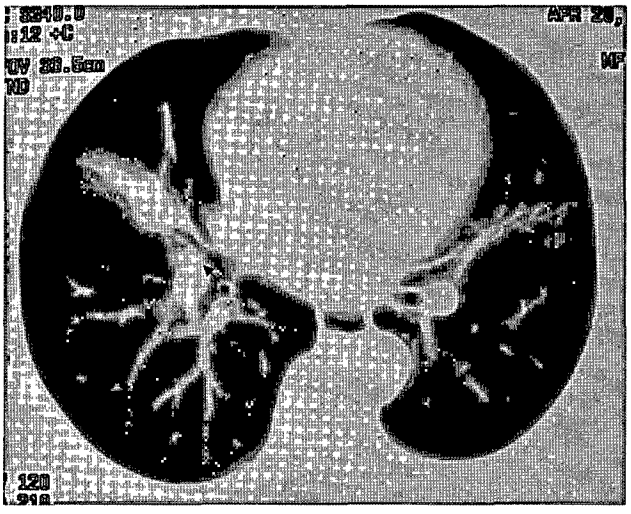

Fig. 3 Segmental atelectasis over right upper lung

Serials of examinations were arranged to evaluate the origin of metastatic adenocarcinoma. Results of tumor markers are as below: CEA =49.92 ng/ml(<5); CA199 <2 U/ml; CA 125=85.8 U/ml (<35); CA153= 70.2 U/ml (<31.3), no monoclonal spike on serum protein electrophoresis. Lower gastrointestinal scopy and biopsy showed hyperplastic polyp of rectum and colon. Upper gastrointestinal scope examination and biopsy showed hyperplastic polyp of duodenum. Tc99M MDP bone scan revealed increase radioactivity in right shoulder, sternum, 4 th throactic veterbrum, sacrum, bilateral sacral-iliac joint, acetabulum, proximal femoral bone, left ankle and occipital bone. Chest CT scan revealed segmental atelectasis in right upper lung field (Fig. 3), cholecystectomy, and no focal mass lesion in liver, and no evidence of ascites or lymphadenopathy. Positron emission tomography showed increased uptake in right upper lung and right hilum lymph adenopathy, which was suspected to be a malignancy. Bone metastasis was also suspected on sacrum, coccyal, bilateral ilium, ischium, right pubic bone, and bilateral femoral head.

Metastatic adenocarcinoma was impressed, adenocarcinoma of lung as the origin was highly suspected but the patient refused to receive bronchoscopic examination to confirm the diagnosis. The development of a malignancy, however, is an indication to discontinue anti-TNF α therapy. She received chemotherapy and radiotherapy in the oncologic department. This patient discontinued Enbrel after using 38 vials in total, but neither the size of tumor nor the general condition improved after discontinuation.

DISCUSSION

Rheumatoid arthritis (RA) patients subjected to prolonged immune suppressive treatment have always been concerned whether the inflammatory disease or its treatment might increase the risk of cancer. According to the British Society for Rheumatology guidelines for prescribing TNF α blockers in adults with rheumatoid arthritis (update of previous guidelines of April 2001) [6], patients should be investigated for potential malignancy if clinically suspected and consideration should be given to stop anti-TNF α treatment if malignancy is confirmed. There have been numbers of malignancies, including lymphoma, reported from studies and post-marketing surveillance in association with the anti-TNF α therapies [7].

The issue of whether treatment with anti-TNF agents poses a higher risk for solid malignancies remains unresolved. The pooled odds ratio for malignancies in anti-TNF–treated patients for malignancy was 3.3 (95% confidence interval [CI], 1.2-9.1), in a meta-analysis study which included nine randomized, placebo-controlled trials of the anti-TNF antibodies in patients with rheumatoid arthritis [8].

In Taiwan, appropriately 500 patients with RA were undergoing etanercept therapy until April 2006 [9], so far there is no post-marketing surveillance study data in Taiwan and no known case reports of cancer after etanercept therapy to our knowledge.

Before initiating Enbrel treatment, this patient was healthy except for the problem of arthritis. No signs of malignancy such as body weight loss, unexplained fever or mass were found, though this patient didn't receive extensive screen examinations for malignancy. There were also no significant side effects during the first course of Enbrel treatment.

The TNF plays a paradoxical role by acting as a tumor necrosis factor and also as a tumor promoting factor in the evolution of cancer [10]. TNF is an inflammatory mediator, with actions directed towards both tissue destruction and recovery. It can induce death of diseased cells at the site of inflammation, and stimulates fibroblast growth [11]. Several clinical studies are underway to assess the role of anti-TNF α therapy in malignancy. Direct evidence for pro-cancer actions of TNF comes from the findings that, mice lacking the gene for TNF are resistant to skin carcinogenesis [12]. High-dose local TNF selectively destroys tumor blood vessels in malignancy. But when given long term, it may act as an endogenous tumor promoter, contributing to the tissue remodeling and stromal development necessary for tumor growth and spread [13].

The role of previous immunosuppressive therapy in developing malignancy in RA patients needs to be considered. There are case reports of lymphoproliferative malignancies in rheumatoid arthritis patients who were treated with methotrexate [14]. This patient received both 5 mg prednisolone and 500 mg salazopyrizen twice a day for about 4 years, 200mg hydroxychloroquine twice a day, and 7.5 mg methotrexate a week for about 2 years. The possibilities that disease-modifying antirheumatic drugs (DMARD) cause cancer in this patient could not be ignored. Besides, patients treated with anti-TNF α agents have more severe disease and greater chronic immune stimulation, which may increase the risk of malignant transformation. This patient suffered from RA for more than 8 years and the DAS 28 score of this patient was above 7 before using Enbrel. In a study from the Norfolk Arthritis Register (NOAR), rheumatoid arthritis itself may play an important role in the etiology of the non-Hodgkin's lymphoma; the increased risk is manifested within the first 5 years [15].

Though this patient didn't receive bronchoscopic biopsy to confirm the origin of metastatic adenocarcinoma, right upper lobe of lung cancer

was highly suspected according to the result of PET scan and chest CT. The major risk factors of lung cancer include tobacco smoke, radon, environmental and workplace carcinogens, nutrition, and genetic susceptibility [16]. This patient didn't smoke, and didn't have any occupational exposure of any carcinogens, or family history of lung cancer. Therefore, being a rheumatoid arthritis patient and biologic treatment are the major risk factors of cancer known in this patient.

One noteworthy clinical feature of this case is the short interval between the initiation of anti-TNF α therapy and the development of malignancy. Of the 26 cases of lymphoproliferative disorders reported to The FDA's passive postmarket adverse event reporting system that occurred following treatment with TNF α antagonists, 14 of them developed lymphoma detected within 8 weeks after initiation of treatment, and in 2 of these patients it remitted after cessation of TNF α antagonist treatment [5]. There is a possibility that this metastatic tumor observed in this case was already present when the biologic treatment was started and have simply been unmasked rather than initiated by the treatment, but neither the size of tumor nor the general condition of this patient improved after discontinuation.

Though there is no clear answer to whether the exposure of Enbrel treatment or the disease of RA itself are related to metastatic adenocarcinoma in this patient, it is still worth reporting the incidental case of malignant disease in patients receiving TNF antagonists, especially after such a short period.

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類風濕性關節炎病患接受抗腫瘤壞死因子治療後發現轉移性腺癌

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一位65歲女性病患經診斷為類風濕性關節炎多年後，經過評估後接受抗腫瘤壞死因子治療。在第一次接受抗腫瘤壞死因子24次治療時，並無重大感染或任何嚴重副作用出現。第二次接受抗腫瘤因子治療時，右臀骨疼痛加劇，X 光發現在腸骨有溶骨性病灶。右臀骨切片病理檢查發現為轉移性腺癌，經過一系列檢查後，胸部電腦斷層發現右上肺葉塌陷，正子斷層造影發現右上肺葉葡萄糖攝取量增加，懷疑是右肺有惡性腫瘤。病人因此停止注射抗腫瘤壞死因子，接受化學和放射治療。類風濕性關節炎接受抗腫瘤壞死因子治療後發現轉移性腺癌，癌症和接受抗腫瘤壞死因子治療以及類風濕性關節炎之間的關係為何，值得進一步研究。

關鍵字：類風濕性關節炎、轉移性腺癌、抗腫瘤壞死因子