

Case Reports

Paraneoplastic arthritis mimicking rheumatoid arthritis in cervical cancer

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Summary

Paraneoplastic arthritis, a subcategory of paraneoplastic syndrome, presents in a similar manner to rheumatic disorder and usually precedes the detection of the primary tumor by years. Herein, the authors report a case of a patient who was diagnosed with paraneoplastic rheumatoid arthritis (RA)-like arthritis with synchronous cervical cancer. A 38-year-old nulligravida woman was admitted to the gynecology department with a three-month history of irregular vaginal spotting accompanied by severe multiple joint pain. She had a one-year history of RA, for which she had been receiving treatment. During the early stage of treatment, her symptoms were slightly improved by RA treatment; however, after eight months of treatment, she showed absolute resistance to RA treatments and complained of a profuse vaginal discharge with severe foul odor. After colposcopy-directed punch biopsy, she was diagnosed with Stage IIA2 squamous cell carcinoma of the cervix. She underwent radical hysterectomy with lymphadenectomy without complications. After treatment, the multiple joint pain associated with paraneoplastic arthritis spontaneously disappeared. There was no evidence of malignancy according to the follow-up cervical cytology report, magnetic resonance imaging, and positron emission tomography-computed tomography.

Key words: Rheumatoid arthritis; Cervical cancer; Inflammation; Paraneoplastic syndromes; Joint diseases.

Introduction

Paraneoplastic syndrome refers to various musculoskeletal syndromes including myopathy and polyarthritis, which are indirectly associated with neoplasms. [1] Paraneoplastic arthritis, a subcategory of paraneoplastic syndrome, presents in a similar manner to rheumatic disorder and usually precedes the detection of the primary tumor by years. [2] Currently, the most common cancers associated with paraneoplastic arthritis have been prostate, breast, and bladder cancers. [1] Paraneoplastic arthritis with synchronous cervical cancer is rare. The authors present a case of paraneoplastic rheumatoid arthritis (RA)-like arthritis accompanied by cervical cancer and its spontaneous regression after cervical cancer treatments.

Case Report

A 38-year-old nulligravida woman was admitted to the present department with a three-month history of irregular vaginal spotting accompanied by severe multiple joint pain. She had a one-year history of pulmonary tuberculosis and RA. Combined agents including steroids and immunotherapy were used to treat symptoms of acute arthritis in multiple joints; however, the symptoms were not subdued even with increased doses. The patient had difficulty with not only activities of daily living but also changing positions without assistance. She had severe erythematous swelling in the left elbow, left wrist, left metacarpal joints, right

second finger joints (metacarpophalangeal and proximal interphalangeal joints), right knee, and right ankle, and a limitation of joint motion caused by pain and edema. In addition, a low-grade persistent fever of 37.7°C lasted for > seven days. C-reactive protein (CRP), white blood cell, and anti-double-stranded DNA antibody levels were increased to 32.8 mg/dl, 15,050/ml, and 28.6 IU/ml, respectively (Figure 1). However, results for the rheumatoid factor (RF) and the anti-cyclic citrullinated peptide (CCP) antibody were negative.

A pelvic examination indicated a slightly enlarged, soft uterus with a 4.0 × 3.0 cm protruding mass in the cervix. A diagnosis of moderately differentiated squamous cell carcinoma was made after colposcopy-directed punch biopsy. Magnetic resonance imaging (MRI) confirmed the existence of a non-homogeneous cervical tumor (4.8 × 3.8 × 3.3 cm) with multiple enlarged lymph nodes (Figures 2A, 2B). There was no evidence of parametrial invasion or distant metastasis. Her clinical stage was cervical cancer IIA2, and levels of serum tumor markers were elevated (squamous cell carcinoma antigen = 12.6 ng/ml, carcinoembryonic antigen = 2.6 ng/ml) (Figure 2C). Radical hysterectomy and pelvic and para-aortic lymphadenectomy were performed. During the operation, chronic pelvic inflammation with pelvic congestion was observed. The uterus was slightly enlarged, and both ovaries, omentum, and other pelvic and abdominal viscera appeared normal. Histopathologic examination disclosed moderately differentiated, large-cell, non-keratinizing squamous cell carcinoma of the uterine cervix with lymph node metastasis (1/39, right external iliac lymph node). Both parametria were unremarkable. On postoperative day 3, the RA symptoms improved, and the CRP level decreased to 0.7 mg/dl. The patient received adjuvant carboplatin and paclitaxel chemotherapy, which was well-tolerated. After completion of chemotherapy, there was no evidence of malignancy on positron emission tomography-computed tomogra-

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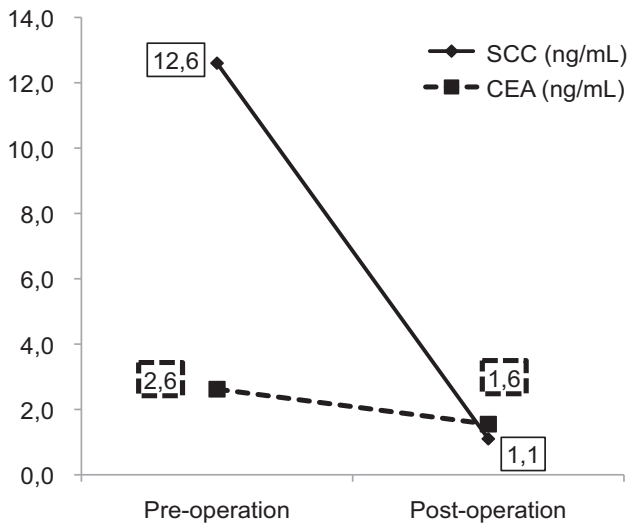


Figure 1. — Serologic markers for cervical cancer (SCC: squamous cell carcinoma antigen - solid line, CEA: carcinoembryonic antigen - dotted line).

phy scanning or MRI, and serum tumor marker levels returned to normal. Furthermore, her rheumatoid symptoms spontaneously regressed. The last day in the hospital, at a follow-up visit, follicle stimulating hormone level was 2.9 mIU/ml.

Discussion

Paraneoplastic arthritis is one of the arthropathies in a spectrum of cancer-associated rheumatic syndromes and is associated with peptide, hormone, and immune complexes secreted by tumor cells. [3] Because paraneoplastic arthritis that is associated with malignancy is usually clinically indistinguishable from RA, [4] it is important to know its clinical features, which are a prelude to hidden neoplasia.

A review of the literature indicated the following characteristics of paraneoplastic arthritis: predominant involvement of a lower extremity, development in elderly patients, explosive onset, asymmetric involvement, absence of rheumatoid factor, no familial history of rheu-

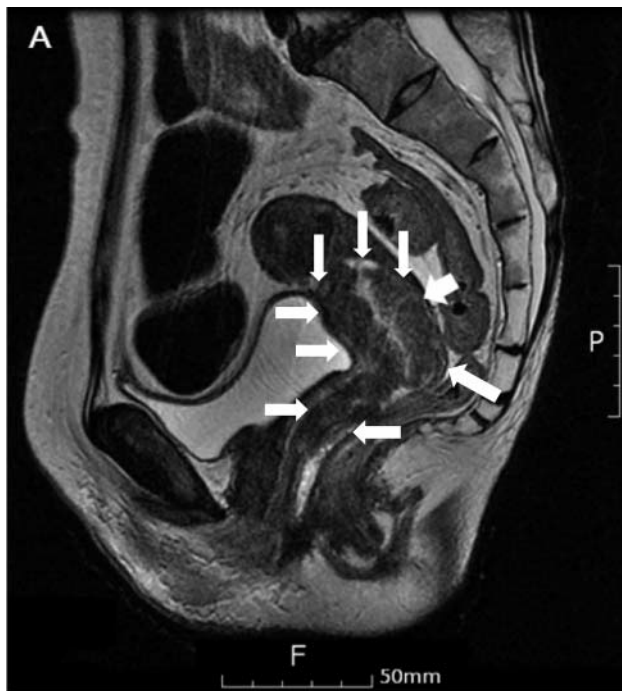
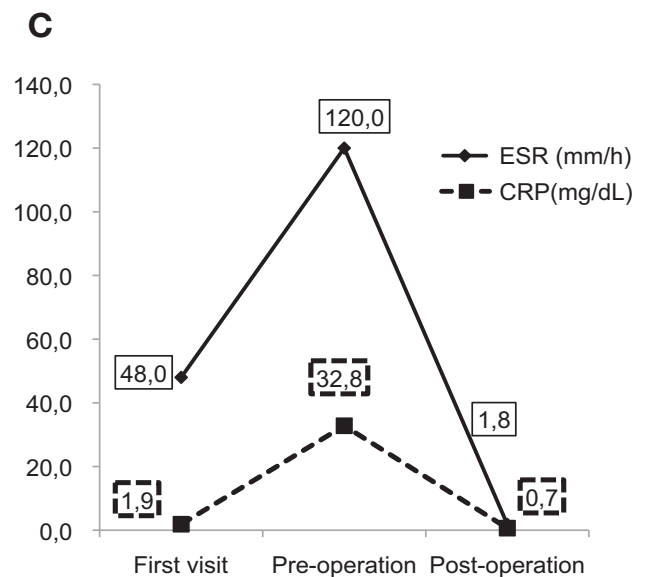
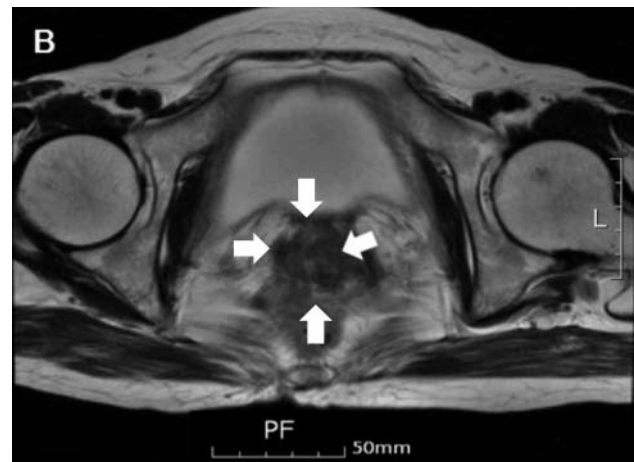


Figure 2A. — Magnetic resonance imaging confirming the existence of 4.8 x 3.8 x 3.3 cm, heterogeneous T2 low signal intensity mass in uterine cervix. The lesion involved upper one-third of vagina. Arrows (white color) indicate cervical cancer mass on T2 weighted sagittal view.

Figure 2B. — Cervical cancer can be noted at T2 weighted axial view (white color arrow).

Figure 2C. — Serologic markers for inflammation (ESR: erythrocyte sedimentation rate - solid line, CRP: C-reactive protein - dotted line).



matic diseases, no evidence of destruction on radiologic imaging, and resistance to standard anti-rheumatic treatment [2, 5, 6].

Initially, the present patient had arthritis of > three joints including the hand and also complained of morning stiffness, which fulfilled the criteria of RA. [7] Serologic tests performed for the diagnosis of RA indicated positive RF and negative anti-CCP results. Similarly, Geng *et al.* reported that 17.6% of RA patients had negative serologic test results. [8] Interestingly, there were several points that supported the diagnosis of paraneoplastic arthritis. She showed refractoriness to classic RA treatment and no improvement with an increased dose of steroids and adjuvant immunotherapy. Because of severe pain in the acute stage that affected the patient's activities of daily living, her hygiene status deteriorated. Moreover, her arthritic symptoms worsened at the time of the diagnosis of cervical cancer. However, joint manifestations disappeared after complete cure of cervical cancer. She had no familial history of rheumatoid arthritis and no joint deformity in imaging studies.

In the present case, concurrent chemoradiation (CCRT) was strongly recommended as a postoperative adjuvant therapy to cure lymph node metastasis. [9] However, the patient received chemotherapy rather than CCRT because she refused to receive radiation treatment. Takeshima *et al.* reported excellent outcomes and tolerable complications with chemotherapy in patients with cervical cancer. They also suggested that chemotherapy could be a potent alternative therapy for high-risk cervical cancer. [10] The presented patient tolerated chemotherapy well. In the present authors' experience, the postoperative follow-up method in patients with cervical cancer and paraneoplastic arthritis was the same as that in ordinary cervical cancer patients.

In conclusion, paraneoplastic arthritis accompanied by cervical cancer is very rare. It can present with deteriorating symptoms such as refractory arthritis and severe joint pain despite appropriate therapy. It cannot be improved unless cervical cancer is completely treated. In patients with acute refractory RA, the presence of additional chronic inflammatory or malignant diseases should be carefully considered.

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References

- [1] Caldwell D. S.: "Musculoskeletal syndromes associated with malignancy". *Semin. Arthritis Rheum.*, 1981, 10, 198.
- [2] Andras C., Csiki Z., Ponyi A., Illes A., Danko K.: "Paraneoplastic rheumatic syndromes". *Rheumatol. Int.*, 2006, 26, 376.
- [3] Naschitz J. E.: "Rheumatic syndromes: clues to occult neoplasia". *Curr. Opin. Rheumatol.*, 2001, 13, 62.
- [4] Kumar S., Sethi S., Irani F., Bode B.Y.: "Anticyclic citrullinated peptide antibody-positive paraneoplastic polyarthritis in a patient with metastatic pancreatic cancer". *Am. J. Med. Sci.*, 2009, 338, 511.
- [5] Sheon R.P., Kirsner A.B., Tangsintanap P., Samad F., Garg M. L., Finkel R.I.: "Malignancy in rheumatic disease: interrelationships". *J. Am. Geriatr. Soc.*, 1977, 25, 20.
- [6] Bahat G., Kamali S., Saka B., Erten N., Karan M.A., Tascioglu C.: "Paraneoplastic arthritis may mimic rheumatoid arthritis with symmetrical and upper extremity predilecting presentation". *J. Clin. Rheumatol.*, 2009, 15, 319.
- [7] Aletaha D., Neogi T., Silman A. J., Funovits J., Felson D.T., Bingham C.O., 3rd, *et al.*: "2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative". *Arthritis. Rheum.*, 2010, 62, 2569.
- [8] Geng Y., Zhou W., Zhang Z.L.: "A comparative study on the diversity of clinical features between the sero-negative and sero-positive rheumatoid arthritis patients". *Rheumatol. Int.*, 2012, 32, 3897.
- [9] Peters W.A., 3rd, Liu P.Y., Barrett R.J., 2nd., Stock R.J., Monk B. J., Berek J.S., *et al.*: "Concurrent chemotherapy and pelvic radiation therapy compared with pelvic radiation therapy alone as adjuvant therapy after radical surgery in high-risk early-stage cancer of the cervix". *J. Clin. Oncol.*, 2000, 18, 1606.
- [10] Takeshima N., Umayahara K., Fujiwara K., Hirai Y., Takizawa K., Hasumi K.: "Treatment results of adjuvant chemotherapy after radical hysterectomy for intermediate- and high-risk stage IB-IIA cervical cancer". *Gynecol. Oncol.*, 2006, 103, 618.

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