

Paraneoplastic Arthritis in Advanced Ovarian Cancer and its Correlation with CA125 and HE4 Levels: A Case Report

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Introduction

Ovarian cancer (OC) is the eighth most common cancer in women, with 313.959 new cases and 207.252 new deaths in 2020 worldwide [1]. It is frequently called the “big silent killer”, since most of the cases become symptomatic and are diagnosed in advanced stages, without any screening program being yet available. Sign and symptoms are absolutely general and vague: abdominal pain, early satiety, changes in bowel habits, abdominal pain [2], thus causing a delayed diagnosis. In extremely rare cases, ovarian cancer can only manifests through a paraneoplastic polyarthritis syndrome [3,4]. To date, only about twenty cases have been reported in literature, the first one in 1966 [5]. The median age of onset is 64 years [4].

Generally speaking, a paraneoplastic syndrome is defined as a disease, which can develop prior or concomitantly with a cancer, but is not due to the local presence of tumor cells. Usually it precedes the diagnosis of cancer by no more than two years and is mostly associated with lung and gastric tumors, while it is very rare in gynecological malignancies [6]. Symptoms are heterogeneous and include endocrine, neurological, vascular or dermatological manifestations [6-8]. Endocrine manifestations should not, by definition, figure in the ovarian cancer paraneoplastic syndrome, since the ovarian tissue regularly produces hormones [8]. The most possible explanation for the paraneoplastic syndrome is an immunological alteration [9].

Concerning OC, circulating immune complexes have been discovered in patients' serum [9]. When they deposit in the glomerulus, a nephrotic syndrome can occur [10]. In addition, several antibodies to a number of tissue antigens have been found in the blood of women affected by OC [11]. These antibodies can explain some rare and extremely unusual OC clinical manifestations, such as cerebellar degeneration or osteoarticular disorders. In fact, the antibodies against Purkinje cells, found in a patient with OC, caused a cerebellar degeneration [12,13]. Other antibodies may provoke, in women affected by OC, a polyarthritis

syndrome, dermatomyositis and polymyositis [4,14,15].

This article describes a case of severe, disabling arthritis in a 60 years old patient affected by advanced serous OC. For the first time, arthritis is correlated to CA125 and HE4, the most promising biomarkers in OC, to monitor the status of the disease.

Case Report

A 60 years old Caucasian woman presented at Campus Bio Medico University of Rome in March 2016 with strong, acute, hand pain (NRS 10) and stiffness, which made it difficult for her to make a fist or hold an object. The pain, arisen in January 2016, involved both arms and shoulders and was sometimes so intense that her movements were totally restricted. Because of the pain, she could not even rest during the night. She presented a deformation of her hands as well: they were edematous, shiny, stiff, white and discoloured. Metacarpophalangeal 2-5 (MCP 2-5) and proximal interphalangeal 2-5 (PIP 2-5) were the most thick and painful joints. In March, her blood exams showed an hemoglobin of 8,2 gr/dl, leucocytes $6.32 \times 10^9/L$, ENA (SSA, SSB, RNP, Scl70), ACA, ANA, FR, Anti-GAD totally negative. Her Body Mass Index was 17. She had no other relevant systemic symptoms. After several investigations, she underwent an abdominal computed tomography scan, which revealed a 10 cm large abdominal mass with some peritoneal and intestine secondaries and ascitis. CA125 was 4532 UI/ml (normally <35 UI/ml), HE4 5430 pmol/L (normally <140 pmol/L). A diagnostic laparoscopy was immediately performed, confirming an advanced, metastatic, serous ovarian cystadenocarcinoma, stage IIIC. Therefore, doctors decided to initiate neoadjuvant chemotherapy with carboplatin and paclitaxel.

Progress The patient referred a clear improvement of her conditions some days after each cycle of chemotherapy, NRS 6, but then the pain and the stiffness worsened again. She tried to control her symptoms with: Fentanyl 25 mcg, Duloxetine 30mg, Tetracosactide acetate 1mg, Oxycodone 10 mg and some physiotherapy. At the end of four cycles of chemotherapy, with

the medications mentioned above, the pain finally ameliorated and remained stable (NRS 6), and her stiffness slightly improved in the following months. Levels of CA125 and HE4 were dosed after each cycle of chemotherapy, and showed a progressive reduction. CA125 was 4532 UI/ml at the beginning, 3903 UI/ml after the 1st cycle, 2465 UI/ml after the 2nd, 1875 UI/ml at the 3rd, 987 UI/ml at the end. HE4 was 5430 pmol/L at the beginning, 4567 pmol/L after the 1st cycle, 3980 pmol/L after the 2nd, 2579 pmol/L at the 3rd, 1256 pmol/L at the end. CA125 and HE4 demonstrated the tumor response to chemotherapy. Unfortunately the patient died before the already scheduled debulking surgery.

Discussion

Paraneoplastic arthritis is a rare and severe condition, which can be associated to ovarian cancer. It has also been described in a wide set of other malignancies such as leukemia, pancreatic adenocarcinoma, lung carcinoma and Hodgkin's disease [16]. Etiology is still unclear. Some possible reasons in OC may be an autoimmune phenomenon [17], or the release of fibrosis enhancing factors, hormones or neuronal factors from tumor cells [4,18]. Bremer was the first scientist to describe a case of bilateral shoulder-hand syndrome linked to ovarian carcinoma in 1966 [5]. Medsger reported a case of polyarthritis, preceding the diagnosis of OC by 5 to 25 months, in 1982 [18]. Since then, a few more articles have shown the association between OC and paraneoplastic arthritis, for a total of about 20 cases to date [3-5,8,17-19]. The differential diagnosis includes many diseases such as rheumatoid arthritis, scleroderma and eosinophilic fasciitis [4]. The literature is unanimous in the conclusion that corticosteroid treatment has a minimal impact on the quality of life and is not able to eradicate the problem [18,19]. Literature also shows the poor prognosis of these patients [4,5,18]. Chemotherapy or debulking surgery could decrease pain and lead to a functional restoration of joints, but are never totally healing [3,19]. Hand therapy is not useful [4]. Our case is similar, since the woman demonstrated a satisfactory improvement of pain and stiffness at the end of the four cycles of neoadjuvant chemotherapy, from NRS 10 to NRS 6. Functional movements were restored, but not totally. These improvements remained stable in the following months, until her death in August 2016. Hand physiotherapy was not helpful; she declared a benefit from the painkillers she was taking.

In this article, for the first time in literature, arthritis was correlated to CA125 and HE4 levels to monitor the status of the disease. CA125 and HE4 were dosed at the beginning and after each cycle of chemotherapy. Their values showed a marked reduction, thus confirming the chemotherapy efficacy. Symptoms improved accordingly. Therefore, the paraneoplastic arthritis returned doubly useful. Firstly, the arthritis partial regression revealed the good response to chemotherapy of the underlying malignancy, taken together with the serum biomarkers CA125 and

HE4. In addition, it anticipated the diagnosis of OC by 4 months, since it was the only symptom complained by the woman. It will be interesting in the future to collect other cases of paraneoplastic syndromes associated with OC, and make a correlation with the onset of the disease and with its response to treatment. For sure, women presenting the symptoms described above, who have high levels of CA125 and HE4, should be immediately screened for ovarian cancer, to get an early diagnosis and urgent treatment.

References

1. (2020) The Global Cancer Observatory - All Rights Reserved.
2. Stewart C, Ralyea C, Lockwood S (2019) Ovarian Cancer: An Integrated Review. *Semin Oncol Nurs* 35: 151-156.
3. Yogarajah M, Soh J, Lord B, Goddard N, Stratton R (2008) Palmar fasciitis and polyarthritis syndrome: a sign of ovarian malignancy. *J R Soc Med* 101: 473-475.
4. Martorell EA, Murray PM, Peterson JJ, Menke DM, Calamia KT (2004) Palmar fasciitis and arthritis syndrome associated with metastatic ovarian carcinoma: a report of four cases. *J Hand Surg Am* 29: 654-660.
5. Bremer C (1967) Shoulder-hand syndrome. A case of unusual aetiology. *Ann Phys Med* 9: 168-171.
6. Ashour AA, Verschraegen CF, Kudelka AP, Kavanagh JJ (1997) Paraneoplastic syndromes of gynecologic neoplasms. *J Clin Oncol* 15: 1272-1282.
7. Morel J, Deschamps V, Toussiot E, Pertuiset E, Sordet C, et al. (2008) Characteristics and survival of 26 patients with paraneoplastic arthritis. *Ann Rheum Dis* 67: 244-247.
8. Hudson CN, Curling M, Potsides P, Lowe DG (1993) Paraneoplastic syndromes in patients with ovarian neoplasia. *J R Soc Med* 86: 202-204.
9. Poulton TA, Crowther ME, Hay FC, Nineham LJ (1978) Immune complexes in ovarian cancer. *Lancet* 2: 72-73.
10. Hoyt RE and Hamilton JF (1987) Ovarian cancer associated with the nephrotic syndrome. *Obstet Gynecol* 70: 513-514.
11. Gerber MA, Koffler D, Cohen CJ (1977) Circulating antibodies in patients with ovarian carcinoma. *Gynecol Oncol* 5: 228-232.
12. Hall DJ, Dyer ML, Parker JC Jr. (1985) Ovarian cancer complicated by cerebellar degeneration: a paraneoplastic syndrome. *Gynecol Oncol* 21: 240-246.
13. Hetzel DJ, Stanhope CR, O'Neill BP, Lennon VA (1990) Gynecologic cancer in patients with subacute cerebellar degeneration predicted by anti-Purkinje cells antibodies and limited in metastatic volume. *Mayo Clin Proc* 6S: 1558-1563.
14. Peters WA 3rd, Andersen WA, Thornton WN Jr (1983) Dermatomyositis and coexistent ovarian cancer: a review of the compounding clinical problems. *Gynecol Oncol* 15: 440-446.
15. Cherin P, Piette JC, Herson S, Bletry O, Wechsler B, et al. (1993) Dermatomyositis and ovarian cancer: a report of 7 cases and literature review. *J Rheumatol* 20: 1897-1899.

16. Pfinsgraff J, Buckingham RB, Killian PJ, Keister SR, Bre- reton WF, et al. (1986) Palmar fasciitis and arthritis with malignant neoplasms: a paraneoplastic syndrome. Se- min Arthritis Rheum 16: 118-125.
17. Vinker S, Dgani R, Lifschitz-Mercer B, Sthoeger ZM, Green L (1996) Palmar fasciitis and polyarthritis associated with ovarian carcinoma in a young patient. A case report and review of the literature. Clin Rheumatol 15: 495-497.
18. Medsger TA, Dixon JA, Garwood VF (1982) Palmar fasciitis and polyarthritis associated with ovarian carcinoma. Ann Intern Med 96: 424-431.
19. Qureshi AA and Saavedra A (2011) Palmar fasciitis and polyarthritis syndrome in patients with ovarian cancer-a case report and review of the literature. Hand (N Y) 6: 220-223.