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# Dermatomyositis as Paraneoplastic Syndrome of Peritoneal and Ovarian Relapse after Long-Term Complete Remission in Patient with Metastatic Bilateral Breast Cancer

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## ABSTRACT

*Dermatomyositis is a rare disease characterised by inflammatory muscle affection and characteristic cutaneous changes. When occurring in a patient with cancer, dermatomyositis may indicate recurrence or progression and poor outcome. Herein, the treatment of metastatic breast cancer, metastatic pattern, characteristics of long-term survivors, and link between dermatomyositis and breast cancer are discussed and the literature reviewed. We report a 57-year old female patient with metastatic bilateral breast cancer whose ovarian and peritoneal relapse after long-term remission was disclosed by occurrence of paraneoplastic dermatomyositis. The patient previously had a 15-year long disease free-period after primary treatment for breast cancer before onset of pulmonary dissemination. Following anthracycline-based chemotherapy, the complete remission lasting another 15 years was accomplished. Dermatomyositis had been resolved upon induction of second-line taxane-based chemotherapy. After completion of six cycles of gemcitabine and paclitaxel chemotherapy, check-up revealed further progression. The patient subsequently underwent six cycles of third-line CAP chemotherapy (cyclofosfamide, doxorubicine, cisplatin) but disease progressed and oral capecitabine chemotherapy was initiated. The patient received four cycles of capecitabine followed by further vast progression and finally expired following massive pulmonary embolism. Our case stresses the need of thorough staging and check-up when dermatomyositis arises in patients with breast cancer, regardless of previous stable long-term complete remission. Furthermore, we believe that treatment with curative intent in young patients with metastatic breast cancer, who have good performance statuses and no comorbidities is required, because it is more likely to produce long-term complete remission. However, following disease relapse a poor outcome can be expected.*

**Key words:** chemotherapy for metastatic breast cancer, long-term complete remission, paraneoplastic dermatomyositis, recurrence of breast cancer

## Introduction

The exact nature of the relationship between dermatomyositis and malignant disease has not been entirely clarified despite numerous studies dedicated to the subject<sup>1</sup>. Tumor types that are likely to be associated with the occurrence of dermatomyositis are ovarian, colorectal, breast and lung cancer<sup>2,3</sup>.

Dermatomyositis can occur prior or simultaneously with the diagnosis of a malignant tumor, but can also be diagnosed in patients after appearance of malignant disease. The severe course of disease is more frequently observed in patients with simultaneous occurrence of dermatomyositis and cancer<sup>4</sup>.

Approximately 30% of breast cancer patients develop local recurrence or metastatic disease, mainly in the first five years with the peak of recurrence rate in the first two years upon completion of the primary treatment. After five years, the annual rates of recurrence rapidly decrease, but due to the fact that small risks still persist, some patients can develop recurrence after a long time period, sometimes even a few decades after the initial treatment<sup>5</sup>. Cases of patients with long-term remission after treatment of metastatic disease are described, but the factors suggesting better outcome remain unclear.

Herein a report of the course of disease in a 57-year old breast cancer patient is presented, with emphasis on simultaneous occurrence of peritoneal dissemination of primary disease and dermatomyositis, which took place almost 30 years after the initial treatment and after 15-years of complete remission. In this patient dermatomyositis was a paraneoplastic manifestation of advanced breast cancer. The modalities of the treatment of metastatic breast cancer were discussed, as well as capabilities and outcome in this rare case of extensive dissemination after a long time period. This case stresses the possibility of dermatomyositis being the first symptom of breast cancer recurrence or progression which then necessitates stage reevaluation and therapy.

## Case Report

Twenty seven year old Caucasian female underwent right breast mastectomy with axillar dissection in 1980 and in 1984 left breast mastectomy with axillary dissection. In both cases early breast cancer was diagnosed, and pathology was ductal invasive carcinoma. After each operation, postoperative radiation therapy to the chest wall with tumor dose of 45 Gy with 2,25 Gy fraction was applied.

Lung dissemination was detected by chest X-ray, in 1995, and consequently, the patient received the first line of chemotherapy with 6 cycles of CAF regimen (cyclophosphamide, doxorubicin, 5-fluorouracil). The therapy resulted in the complete regression of pulmonary metastases, with no evidence of disease on radiological imaging. Within the follow up period of fifteen years, no sign of disease recurrence was observed on regularly attended follow up.

In 2008, the patient underwent resection of right kidney due to localised kidney tumour, which was detected on regular abdominal ultrasound. Pathology report revealed T1NxM0 kidney adenocarcinoma. There were no signs of recurrence nor dissemination at the time of the surgery or during the entire subsequent follow up period.

In February 2010, the patient consulted a dermatologist due to eyelid edema and erythematous changes on exposed parts of the skin with proximal muscle weakness (Figure 1). The level of creatine kinase (CK), and electromyography (EMG) report were normal, but deltoid muscle biopsy revealed inflammatory myopathy. After consulting the clinical immunologist, diagnosis of paraneoplastic dermatomyositis was reached.



Fig.1. Eyelid edema.

Patient was not given steroid pulse therapy due to the inactivity of disease and normal findings of CK and EMG. Simultaneously with the occurrence of dermatomyositis, the tumor in projection of the right ovary and multiple nodules in the peritoneum suspicious for metastasis were detected on abdominal ultrasound. Levels of tumor markers were considerably elevated: CA 15-3 was 240,2 U/mL and CA-125 was 3472 U/mL. Explorative laparotomy was performed. Extensive dissemination encompassing ovaries, omentum and peritoneum was found and bilateral adnexectomy and omentectomy were performed. Regression of cutaneous changes immediately followed.

Pathology report based on morphology and immunohistochemical profile of resected adnexa, omentum and peritoneum, strongly suggested the dissemination of breast cancer (immunohistochemical analysis revealed strong positive reaction for estrogen receptor, positive reaction for epithelial membrane antigen (EMA) and cytokeratin 7 (CK7), while the reaction for progesterone receptors, vimentin, CD 10, pan-CK and HER2 was negative).

A second-line of breast cancer chemotherapy, six cycles of paclitaxel and gemcitabine, were applied. Consequently, tumor markers levels significantly decreased (CA 15-3 from 199,4 U/mL to 97,6 U/mL and CA 125 from 3335 U/mL to 1346 U/mL). Clinical status improved and cutaneous changes withdrew.

As a part of follow up, computed tomography (CT) of the abdomen and pelvis was performed in July and October 2010. The first CT showed stable disease while the second one revealed the disease progression with peritoneal carcinosis, multiple omental nodules, and extensive ascites. Tumor markers were again elevated (CA 15-3 was 599,7 U/mL and CA-125 was 15207 U/mL).

Third-line CAP chemotherapy (cyclophosphamide, doxorubicin, and cisplatin) was applied through 6 cycles, followed by further progression (abundant ascites, large omental deposits). The patient remained in relatively good performance status and therapy proceeded with four cycles of oral chemotherapy with capecitabine, with no side-effects. Unfortunately, the patient experienced vast progression, general condition deterioration and expired following massive pulmonary embolism. The patient died altogether two years after the onset of ovarian and peritoneal dissemination.

## Discussion

The connection between dermatomyositis and malignancy has been widely addressed in medical literature. Nevertheless, dermatomyositis is mostly diagnosed in non-cancer patients. Dermatomyositis occurring in patients with no history of cancer could be a paraneoplastic feature of underlying malignancy or indicate cancer recurrence in the case of complete remissions after previous systemic treatment<sup>6</sup>. Exact mechanisms behind the connection of dermatomyositis and cancer are still not clarified. Clinical course of dermatomyositis regularly follows the course of coexisting cancer, so after resection or successful systemic treatment of primary cancer, symptoms of dermatomyositis mostly subside and likewise, symptoms reappear in case of tumor relapse or progression<sup>7</sup>.

The patient reported in this case is specific due to several reasons. Firstly, the patient was diagnosed with bilateral breast cancer. Secondly, after eleven years of a complete disease free interval following primary treatment, disease relapsed in form of multiple metastatic pulmonary nodules occurred. Third, anthracycline-based chemotherapy (CAF) produced a fifteen year-long remission. Fourth, the patient developed a second primary kidney cancer. Fifth, dermatomyositis revealed disease recurrence in the form of multiple metastatic lesions in both ovaries and peritoneum, histologically proven to be a spread of primary breast cancer. Sixth, there was no elevation of CK or impairment of EMG, which is uncommon for paraneoplastic dermatomyositis.

The majority of breast cancer recurrences occur in the first 5 years after primary therapy and in that subset most recurrences happen in first two years after surgery. After the first 5 years, the percentage of recurrence slowly decreases for the next 12 years. Recurrence can occur even ten years after primary treatment but that is very rare<sup>5</sup>. In our patient, cancer recurred eleven years upon completion of primary treatment, which can be considered as exceptional.

The course of dermatomyositis is often identical to those of primary breast cancer. In a report by Osako, CK as marker of dermatomyositis activity was elevated during cancer diagnosis, dropped after primary resection and increased in parallel with the development and progression of distant metastases<sup>8</sup>. In our case, the CK level was normal probably because there was no significant muscle

destruction seen on biopsy and in our patient dermatomyositis was without corresponding laboratory indicators and the only sign of disease were skin changes and weakness of proximal musculature. Nevertheless, in our patient dermatomyositis indicated breast cancer recurrence in a form of peritoneal and ovarian metastases and after the patient underwent surgery, symptoms subsided. There are reports that in patients with dermatomyositis associated with breast cancer, check-up of metastatic spread or new ovarian cancer is necessary<sup>9</sup>. In our case, simultaneously with onset of dermatomyositis, immediate patient check-up for distant recurrence was undertaken which revealed ovarian and peritoneal recurrence. This is in accordance with reports in the literature, where flare-up of dermatomyositis is often a sign of breast cancer recurrence<sup>10</sup>.

Median survival for patients with metastatic breast cancer ranges between 2 and 4 years, however, a minority of patients survive longer than 3 to 5 years. Some patients who achieve a complete remission after chemotherapy remain in this state for prolonged periods of time, even beyond 20 years<sup>11–13</sup>. We analysed two reports which dealt with characterization of complete responders to chemotherapy for metastatic breast cancer and encompassed longer follow-up data than in other trials (even 15 years). Analysis indicated that 20% of women with metastatic breast cancer who have achieved a complete clinical remission were alive and disease-free at five years. Anthracycline chemotherapy is linked with a longer disease-free interval after the complete response along with longer survival<sup>14</sup>. Likewise, Falkson et al. found that premenopausal women with metastatic breast cancer, with a good performance status or with estrogen-receptor positive tumors, who were treated with oophorectomy plus anthracycline chemotherapy, survived close to five years<sup>15</sup>. These long-term survivors, compared to overall complete responders and the total patient population have some common characteristics: they are usually young, have excellent performance status, and have limited metastatic disease. Although this fraction represents a small subgroup of patients (between 1% and 3%), this finding put in question the commonly held belief of the inevitably adverse course of metastatic breast cancer<sup>16,17</sup>. In this report anthracycline-based chemotherapy is used as first-line treatment what is nowadays beside taxane-based combination chemotherapy considered as the main chemotherapy backbone for HER2-negative metastatic breast cancer. In chemotherapy treatment of women with metastatic breast cancer, the most effective is first-line chemotherapy, while the efficacy of second and subsequent lines is uniformly poor<sup>18</sup>. In work done by Greenberg et al, six subgroups of patients with pulmonary metastases as the only site of disease out of total of 263 patients living in long-term complete remission were identified, who were treated with chemotherapy and/or hormonotherapy. One of these six subgroups, which involved 21 patients had the longest duration of complete remission of even 231 months (more than 19



years)<sup>16</sup>. This is very indicative, since our patient also had a single site of disease – pulmonary metastases only.

The most common sites for breast cancer metastasis include the bone, lung, liver, lymph nodes, chest wall, and brain. However, case reports have documented breast cancer dissemination to almost every organ in the body. In one large autopsy series the peritoneum was involved in 25% cases<sup>19</sup>.

When discussing the aims of metastatic breast cancer treatment, several aspects could be identified: the need to prolong life, decrease tumor burden, reduce cancer-related symptoms and maintain of quality of life and function. In a metastatic setting, therapy is not generally considered curative. Numerous studies demonstrated that patients who have received less anticancer therapy, have a longer disease-free interval since initial diagnosis, soft tissue or bone metastases, fewer symptoms and better performance status, and tumors that are hormone-receptor positive are likely to experience longer survival with metastatic disease than more aggressively treated patients (shorter intervals between treatments), visceral metastases, and greater symptomatology<sup>20</sup>. Long-term disease-free survivors are younger and healthier than the overall patient population, have fewer sites of metastasis, and smaller disease volumes. The largest analysis

of long-term responders found that 55% of long-term complete responders had only one disease site, compared with 29% of the total population: 66% of those in complete remission for more than 5 years had lower tumor burden in contrast with 24% in the general patient population<sup>21</sup>.

## Conclusion

Our patient in moment of dissemination had a low tumor burden, was young, premenopausal, with no comorbidity, in excellent performance status and had a long recurrence-free period after primary treatment. All listed factors indicated favourable outcome. It is worthwhile to identify such a metastatic breast cancer population where treatment with curative intent can enable a durable response. However, when disease finally relapses, second and subsequent chemotherapy lines have no effect and a poor outcome is foreseen.

Furthermore, regardless of breast cancer stage or no previous history of cancer, new onset of dermatomyositis is always suspicious for both occult cancer or cancer recurrence no matter how long the remission endured and clinical measure should be undertaken to adequately stage and treat the patient.

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## DERMATOMIOZITIS KAO PARANEOPLASTIČKI SINDROM PERITONEALNOG I OVARIJALNOG RELAPSA NAKON DUGOG PERIODA POTPUNE REMISIJE U BOLESNICE S METASTATSKIM BILATERALNIM RAKOM DOJKE

### SAŽETAK

Dermatomyozitis je rijetka bolest karakterizirana upalnim promjenama u mišićima i karakterističnim kožnim promjenama. Kada se pojavi u bolesnika s rakom, dermatomyozitis može upućivati na povrat ili progresiju maligne bolesti te često ukazuje na loš ishod. U ovom radu opisali smo povezanost između dermatomyozitisa i raka dojke, te raspravili mogućnosti liječenja metastatskog raka dojke, kao i značajke bolesnica koje smatramo izliječenima – tzv. »long-term survivors«. Prikazujemo slučaj 57-godišnje bolesnice s metastatskim bilateralnim karcinomom dojke u koje je pojava paraneoplastičkog dermatomyozitisa u podlozi razotkrila recidiv osnovne bolesti u jajnicima te po peritoneumu. Bolesnica je prethodno imala 15 godina dugo razdoblje bez znakova bolesti po završetku primarnog liječenja, nakon čega je nastupila plućna diseminacija. Po provedenoj kemoterapiji baziranoj na antraciklinima nasupio je kompletan odgovor (remisija) koja je trajala 15 godina, nakon čega je nastupila prethodno opisana diseminacija u područje jajnika te peritoneuma. Dermatomyozitis se povukao po uvođenju druge linije kemoterapije bazirane na taksanima. Po kompletiranju šest ciklusa kemoterapije gemcitabinom i paklitakselom, obrada je ukazala na daljnju progresiju bolesti. Bolesnica je potom primila šest ciklusa treće linije kemoterapije po CAP protokolu (ciklofosfamid, doksorubicin, cisplatin), no bolest je progredirala i započeta je peroralna kemoterapija kapecitabinom. Bolesnica je primila četiri ciklusa terapije kapecitabinom, nakon čega je nastupila daljnja opsežna progresija te je bolesnica konačno preminula pod slikom masivne plućne embolije. Ovaj slučaj ukazuje na potrebu temeljitog „staginga“ i kliničke obrade u slučaju pojave dermatomyozitisa u bolesnica s rakom dojke, bez obzira na prethodnu trajnu i stabilnu kompletnu remisiju. Nadalje, držimo da je u mladih bolesnica s metastatskim rakom dojke koje su dobrog općeg stanja i nemaju komorbiditeta potrebno liječenje s kurativnom namjerom, jer je moguće da se takvim liječenjem postigne dugotrajna kompletna remisija. Ipak, ako konačno dođe do povrata bolesti (relapsa), očekuje se loš ishod.