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Case Report

A case of Miller Fisher syndrome during preoperative chemotherapy for breast cancer

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Abstract: A 53-year-old woman with breast cancer received FEC treatment (5FU: 500 mg/m^2, epirubicin: 100 mg/m^2, and cyclophosphamide: 500 mg/m^2) every 3 weeks as preoperative chemotherapy. Fifteen days after her third cycle of FEC, she developed a cold. Diplopia occurred 4 days after developing the cold, and progressive paresthesia of the hands and weakness of the limbs occurred. She had ophthalmoplegia, ataxia, and are flexia and was diagnosed with Miller Fisher Syndrome (MFS). The cause of MFS during chemotherapy is believed to be caused by an immunological response to infection, or drug neurotoxicity. In our case, since the patient underwent an antecedent upper respiratory infection in the period of myelosuppression, her MFS was probably induced by the immunoreaction associated with this infection. Our patient underwent intravenous immunoglobulin therapy. After initiation of the treatment, her neurological symptoms improved, then, she received a fourth cycle of FEC and her remaining neurological symptoms did not worsen. Thus, we report a rare case of MFS developed in immunosuppression by chemotherapy and remind physicians of the alarming triad of MFS symptoms.

Keywords: Chemotherapy, Miller Fisher syndrome, breast cancer, FEC treatment, diplopia, ophthalmoplegia, myelosuppression, immunological response, upper respiratory infection, drug neurotoxicity

Introduction

MFS has been associated with immunoreaction. However some drugs have been reported to cause neuropathy like-MFS directly. It is important to determine the cause of neuropathy during drug therapy, because the treatment for neuropathy is different depending on the cause.

Case report

A 53-year-old woman underwent a mammography, which revealed a left breast mass. Following a multimodal examination, a biopsy was performed. She was diagnosed with triple-negative breast cancer showing negativity for estrogen receptors, progesterone receptors, and HER2. Clinically, the cancer was evaluated as being at stage I (T1cN0M0).

We recommended that it was better for her to first undergo four cycles of FEC (5FU: 500 mg/m^2, epirubicin: 100 mg/m^2, and cyclophosphamide 500 mg/m^2), four cycles of docetaxel, and only then undergo surgical treatment. She presented with grade 1 nausea during her first and second cycles of FEC but did not have any other adverse events from the treatment. The tumor in her breast decreased to 40% of its initial size, and the therapeutic effect was evaluated as a partial response after two cycles of FEC. On the 15th day of the third FEC cycle, she developed slight fever with chills and a sore throat. Her fever and sore throat lasted for 3 days, i.e., 18 days into the third FEC cycle, and she then visited a medical clinic. She was prescribed acetaminophen, cefditoren pivoxil, ambroxol hydrochloride, tipepidine hibenzate, and sodium azulene sulfonate hydrate, which she took twice. On the 19th day after the third FEC, she devel-

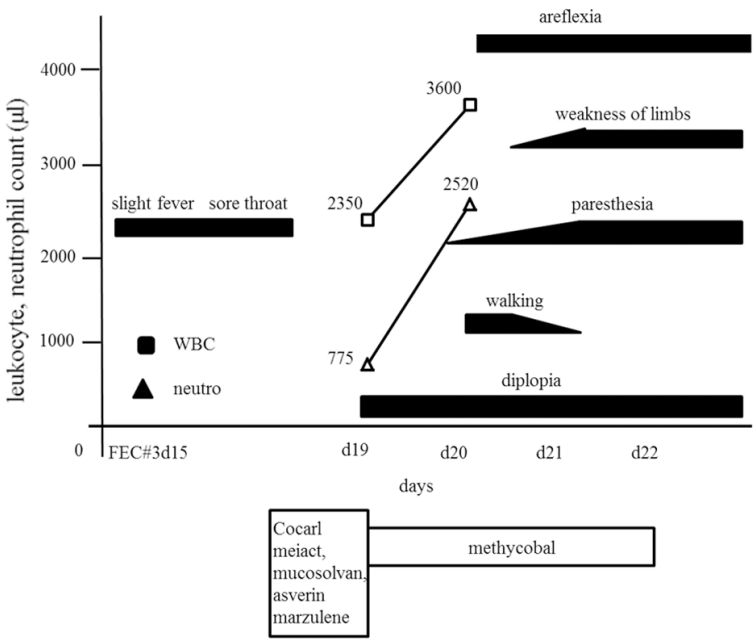

Figure 1. Clinical course from having a cold up to neurological symptom occurrence. Diplopia first occurred 4 days after catching a cold. Paresthesia, areflexia, and weakness of limbs occurred subsequent to diplopia. Finally, she became unable to walk. Slight reductions in leukocyte and neutrophil counts were observed when diplopia occurred; this became normal the next day.

oped diplopia that was worst in a right lateral gaze. Over the next 2 days, she presented with multidirectional diplopia. She subsequently developed paresthesia and hypoesthesia in her hands and feet, but did not complain of headache. She was admitted to our hospital due to gait instability 4 days after her first diplopic symptom. Physical neurological examination revealed that she was exhibited nearly complete ophthalmoplegia. She had no muscle weakness, but did have areflexia in all limbs, truncal ataxia, and was not able to walk independently. No autonomic dysfunction was noted. Her brain magnetic resonance imaging findings were normal. Blood levels of vitamin B1 and acetylcholine receptor were normal. The next day, she presented with multidirectional diplopia, sensorineural right deafness, and areflexia of the limbs. Her symptoms progressively worsened; paresthesia of the upper limbs and hypesthesia of all four limbs occurred within 3 days of her diplopia. She described her paresthesia as feeling as though her hands were covered with something thin and complained that it was strongest around her palms. Her neurological symptoms got worse and she was not able to walk on the 4th day after the onset of her diplopia. It is well known that paraneoplastic neurological syndrome (PNS) occurs most frequently in small cell lung cancer but also occurs in breast cancer [1]. Since the symptoms of PNS vary by their site of disturbance, it was difficult to exclude PNS by either her symptoms or her clinical course. We subsequently performed a cerebrospinal fluid examination that showed normal cell count (1/mm^3) and normal protein amount (25 mg/dl), 1 week after protein amount was increased (83 mg/dl). Ophthalmoplegia, ataxia and areflexia that were developed after respiratory infection and cerebrospinal fluid findings met the feature of MFS. She was thus diagnosed with MFS and hospitalized (**Figure 1**).

The patient was treated with intravenous immunoglobulin therapy (IVIg) for 5 days. After initiation of the treatment, her paresthesia and areflexia slightly improved. She started gait training with a supportive device on the 9th day after the onset of diplopia. On 12th day after the onset of diplopia, the patient developed paralysis of the right facial nerve and right arm, and we became anxious that her condition was deteriorating. However, these symptoms gradually improved, as did the other symptoms, without additional IVIg. She became able to walk on the 28th day after the onset of diplopia. Moreover, she did not experience diplopia when she looked forward. A reduced volume of FEC (80% dose) was administrated 36 days after the onset of diplopia in order to treat the patient's breast cancer. After that, her neurological symptoms did not worsen, and she was discharged 48 days after the onset of her condition. At that time, her vertical eye movement had improved, and she was able to walk without any assistance or supportive device. We decided to suspend her docetaxel (DOC) treatment, which was originally planned to be administered sequentially after the FEC in a preopera-

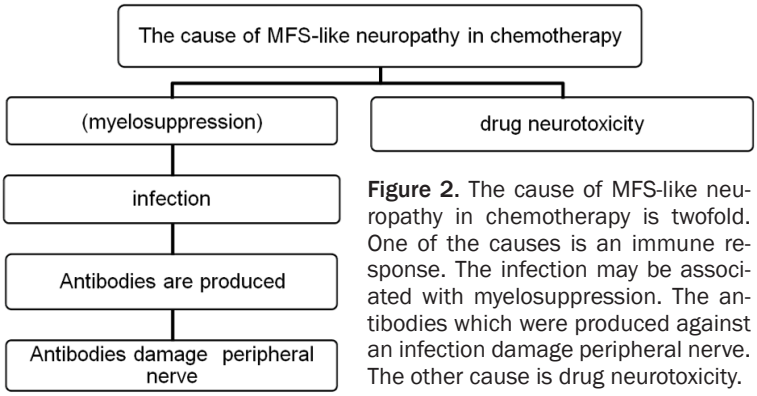

Figure 2. The cause of MFS-like neuropathy in chemotherapy is twofold. One of the causes is an immune response. The infection may be associated with myelosuppression. The antibodies which were produced against an infection damage peripheral nerve. The other cause is drug neurotoxicity.

tive setting. Four cycles of FEC treatment had already decreased the tumor to 58% of its initial size. The patient underwent a breast-conserving lumpectomy and sentinel lymph node biopsy 79 days after the onset of her diplopia. Histological examination of the surgical specimen after preoperative chemotherapy showed an invasive ductal carcinoma, with an invasive size of 0.5 × 0.5 × 0.4 cm and no lymph node metastasis. Histological therapeutic effect was evaluated as Grade 3 according to the Miller-Payne grading system. In detail, degeneration of cancer cells was observed in one- to two-thirds of samples. Because there was no lymph node metastasis, we omitted the DOC treatment.

The patient's latest visit to our hospital was 280 days after the onset of her diplopia, and she presented no signs of breast cancer recurrence. She did show slight diplopia that was gradually getting better.

Discussion

MFS is a variant of GBS and is characterized by the triad of ataxia, areflexia, and ophthalmoplegia. Seventy six percent of MFS patients experience an upper respiratory infection or diarrhea as antecedent infections [2]. It is considered that a cross-reaction by antibodies produced against an infection induces MFS. Presenting symptoms and a recent history of infection are thus the most alarming signs for physicians to suspect. Furthermore, anti-GQ1b antibodies, which were not measured in our case, are possible diagnostic marker of MFS patients [3].

Drug toxicity induces nerve disorder. Interferon alpha, tumor necrosis factor alpha antagonist therapy, antiviral medication, anticancer drugs, and new quinolone were also reported to cause peripheral neuropathy, which could cause GBS (MFS)-like neuropathy [4]. In the anti-cancer agent, vincristine has been reported to induce disorders of sensation and movement [5]. There are two possible mechanisms for MFS-like neuropathy during chemotherapy: an immunological response, which may be associated with myelosuppression, and drug neurotoxicity (**Figure 2**). In the former, almost all patients have a recent history of infection or vaccination before MFS. The absence of an infection reduces the likelihood of GBS [5]. In the latter mechanism, drugs directly damage the peripheral nerve. Changes in the neurological symptoms is linked to the use of the drug can be seen [6], and a physician discontinues the medication. In our case, since the patient underwent an antecedent upper respiratory infection in the period of myelosuppression, her MFS was probably induced by the immunoreaction associated with this infection. The fact that the FEC regimen contains no drugs that have been reported to cause MFS-like neuropathy would also support this estimation. We expected that the reduced volume of FEC decreased the risk of infection and MFS, and thus performed a 4th cycle of FEC. Granulocyte colony-stimulating factor (G-CSF) can shorten periods of myelosuppression and significantly decrease the incidence of febrile neutropenia [7].

In conclusion, we reported a patient who experienced MFS as an adverse event of chemotherapy. Although it happens rarely, GBS (MFS)-like neuropathy could be caused by various drugs. Additionally, MFS was developed among the immunosuppressive state by chemotherapy. Here, we report this case in an attempt to increase awareness among physicians.

Disclosure of conflict of interest

None.

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