Adult Onset Still’s Disease as a Paraneoplastic Syndrome
A Case Report and Review of the Literature

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Abstract
Adult onset Still’s disease (AOSD) is a systemic inflammatory disease with unknown etiology and characterized by evanescent salmon pink rash, sore throat, liver dysfunction, lymphadenopathy, hepatosplenomegaly, arthritis, and leukocytosis. It is a diagnosis of exclusion; however, there are case reports in the literature about patients with malignancies and AOSD-like signs and symptoms. Here we report a patient with AOSD seems to be associated with sarcomatoid renal cell carcinoma. This phenomenon is not distinguishable from primary AOSD either in presentation or in treatment; except for the main purpose of the management should be targeted to the underlying malignancy.

Adult onset Still’s disease (AOSD) is a systemic inflammatory disease with unknown etiology resembling the systemic form of juvenile rheumatoid arthritis. In addition to the high spiking fever, it is characterized by evanescent salmon pink rash, sore throat, liver dysfunction, lymphadenopathy, hepatosplenomegaly, arthritis, and leukocytosis. Since it has no pathognomonic clinical or laboratory signs, its diagnosis is one of exclusion. Along with the infections, malignancies consist of major concern in differential diagnosis. Although the diagnosis of AOSD necessitate to exclude neoplasm, there are case reports suggesting the presence of AOSD or an AOSD-like syndrome in the course of various malignant diseases including leukemia, lymphoma, breast cancer, esophageal cancer, lung cancer, and thyroid cancer. On the other hand, it is controversial whether this phenomenon is a coincidental process or a paraneoplastic condition. Here we are presenting a patient with sarcomatoid renal cell carcinoma (RCC) who also displays symptoms and signs consistent with AOSD, and to our knowledge, this is the first case reporting this co-occurrence.

Case
A 69-year-old man with a 2 month history of fever was admitted to our hospital on June 2012. He had been followed with a diagnosis of chronic renal failure (CRF) due to polycystic kidney disease for 7 years and received hemodialysis. In a routine follow-up, a renal mass had been detected, and a left nephrectomy was performed approximately 3 months before admission to our hospital. The diagnosis of sarcomatoid RCC was made by pathological evaluation. Nearly one week after the operation, symptoms including fever, sweating, and chill appeared. Initially, these symptoms were intermittent but became continuous almost after the first month. He had been hospitalized at another hospital and administered various antibiotics with several diagnoses, such as respiratory and urinary tract infections, with no response. He was discharged from that hospital upon his own request and transferred to ours. At admission, he had remittent fever reaching up to 39.8°C, fatigue, and lethargy. In the physical examination, conjunctival pallor, hepatomegaly, splenomegaly, and axillary lymph node enlargement was found along with fever. He had evanescent skin rash in all extremities. Besides, his metacarpophalangeal, proximal interphalangeal and wrist joints were swollen and tender bilaterally. In his complete blood count, leukocytosis with left shift (31,500/mm³, with 86% neutrophils), anemia (hemoglobin: 8.0 gr/dL), and thrombocytosis (457,000/mm³) were detected. Evaluation...
of blood biochemistry was consistent with CRF; the creatine and blood urea nitrogen levels were 4.75 mg/dL and 75 mg/dL, respectively. Except for hypoalbuminemia, other biochemical tests were within normal limits, including liver function tests. Acute phase reactants including erythrocyte sedimentation rate and C-reactive protein were elevated (140 mm/h and 424.2 mg/dL, respectively). Given the fever, leukocytosis, and the history of surgical intervention, ultrasonography was performed to exclude intra-abdominal abscess formation, which revealed multiple cysts in the liver and right kidney, and hepatomegaly and splenomegaly (long axes were 172 and 144 mm, respectively). The blood, sputum, pharynx swab, and urine cultures were obtained; empirical antibiotic treatment was started with meropenem (500 mg/d) and teicoplanin (400 mg/72 hours). Because of the lethargy and confusion, computed tomography of the brain and lumbar puncture were performed and found normal. All cultures were negative, and the symptoms did not respond to this treatment. Etiologic investigations for anemia disclosed markedly elevated serum ferritin levels (4,815 ng/ml, normal range 22 to 322 ng/ml). Meantime, his repeated cultures were found negative, and anti-fungal treatment was begun, while without any response. Positron emission tomography was performed, which showed an increased activity in the right renal region and intestines that were considered as due to primer or metastatic lesions of the primary tumor. Because his fever was unresponsive to antibiotics, hyperferritinemia and splenomegaly, AOSD, and hemophagocytic lymphohistiocytosis were considered in the differential diagnosis. Autoantibodies, rheumatoid factor, and other immunologic markers, including MPO-ANCA and PR3-ANCA, were negative. Fibrinogen, triglyceride levels, hepatic function tests were normal, and no cytopenia was detected except for anemia. Bone marrow aspiration, biopsy, and a culture were obtained. The culture was negative, and there was no malignant infiltration or hemophagocytosis. Therefore, the diagnosis of hemophagocytic lymphohistiocytosis was less likely. The patient was fulfilling the criteria for AOSD as suggested by Yamaguchi (fever, leukocytosis, lymphadenopathy, splenomegaly, and serologic tests were negative). Actually, these criteria necessitate the exclusion of malignancy. However, since the symptoms and laboratory findings were highly suggestive of AOSD, the patient was diagnosed as paraneoplastic syndrome with AOSD-like features, and a moderate dose of corticosteroid (30 mg/day, methyl prednisolone) was administered. His fever, arthralgia, skin rash, and fatigue resolved immediately, and acute phase reactants decreased. He was discharged after the planning of chemotherapy with interferon.

**Discussion**

Renal cell carcinoma (RCC) originates from the renal cortex and constitutes approximately 80% of primary renal neoplasms. Signs and symptoms of the disease can vary. The classic triad is flank pain, hematuria, and a palpable abdominal mass, although it is not common. On the other hand, many patients with RCC present with or subsequently develop paraneoplastic syndromes including anemia, fever, hypercalcemia, erythrocytosis, thrombocytosis, and AA amyloidosis. The association between rheumatic diseases and malignancy is somewhat complicated. Numerous rheumatic diseases can accompany, predate, or succeed to an underlying malignancy. It has been suggested that rheumatic disorders associated with malignancy can be classified as; 1. musculoskeletal disorders due to direct involvement of bones, joints, or muscles; 2. paraneoplastic syndromes; 3. altered immune system causing both the musculoskeletal and the neoplastic diseases; and 4. adverse reactions to anticancer therapy. In the meantime, several rheumatic diseases, such as rheumatoid arthritis, Sjögren’s syndrome, dermatomyositis, appear to predispose the development of malignancy, especially lymphopoetic and hematopoetic malignancies. On the other hand, some of them occur in a paraneoplastic fashion. Paraneoplastic rheumatic disorders can be defined as “signs and symptoms, which occurred in the course of malignant disease and induced by hormones, peptides, antibodies or other mediators rather than primary tumor or metastases.” There is a wide range of paraneoplastic rheumatic disorders reported in the literature including myopathies, vasculitis, polymyalgia rheumatica, polyarthritis, and lupus-like syndromes. However, malignancy associated AOSD is somewhat rare and little is known about it.

AOSD is a rare systemic inflammatory disease and characterized by spiking fever, evanescent salmon-pink maculopapular rash, arthritis, and leukocytosis with left-shift. Other common clinical findings consist of sore throat, abnormal liver function tests, lymphadenopathy, and splenomegaly. Hyperferritinemia is an important laboratory test that supports the diagnosis of AOSD in an appropriate clinical setting. Nevertheless, the diagnosis of this entity depends on the exclusion of malignant, infectious, and other rheumatic disorders. Exclusion of malignancy is of special concern, and all malignant diseases especially lymphomas, solid cancers, and myeloproliferative disorders should be taken into account. There have been several cases in literature reporting patients presented with AOSD-like symptoms in association with neoplastic diseases.

We have reported a patient with RCC presented with signs and symptoms highly suggestive of AOSD. There is an ongoing debate about the co-occurrence of AOSD and solid cancers; it is controversial whether it is a paraneoplastic syndrome or just a coincidence. Indeed, it is not easy to distinguish them. One can speculate that if the corticosteroid treatment could resolve the symptoms, the possibility of coincidence is more reasonable. However, it is not always the case in AOSD, considering the patients necessitating agents other than corticosteroids, such as anti-TNFs, interleukin-1 and 6 blockers, to resolve their symptoms. On the contrary, given the fact that paraneoplastic syndromes occur due to
the effects of certain mediators, these mediators might also be involved in the development of paraneoplastic AOSD. Therefore, having a good response to corticosteroids in such a scenario would not be an unexpected situation.

In literature, there are 15 cases with AOSD-like disorder associated with malignancies including breast carcinoma, lung carcinoma, thyroid papillary carcinoma, esophageal carcinoma, and some hematologic malignancies<sup>1-15</sup> (Table 1). Some of them precede or occur at the same time with the diagnoses of malignancies, whereas others manifest afterward. Commonly encountered clinical (fever, sore throat, arthralgia, arthritis, and rash) and laboratory (leukocytosis, increased acute phase reactants, and hyperferritinemia) features of malignancy associated AOSD were similar to primary AOSD. All of the cases responded to high-dose corticosteroids or chemotherapy regimens consisting of corticosteroids. In these published cases, almost all of the patients’ AOSD-like symptoms occurred simultaneously with the underlying neoplasm or its relapse. The cases reporting neoplasms that occurred after the diagnosis of AOSD

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Sex</th>
<th>Age</th>
<th>Clinical features</th>
<th>Diagnosis Time</th>
<th>Treatment</th>
<th>Course of AOSD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast cancer&lt;sup&gt;1&lt;/sup&gt;</td>
<td>F</td>
<td>52</td>
<td>spiking fevers, transient macular rash, myalgia, arthralgia, sore throat</td>
<td>At the same time</td>
<td>Aspirin lumpectomy and lymph node dissection</td>
<td>Responded to aspirin After surgery, complete remission despite cessation of aspirin.</td>
</tr>
<tr>
<td>Breast cancer&lt;sup&gt;2&lt;/sup&gt;</td>
<td>F</td>
<td>49</td>
<td>intermittent fever, polyarthralgias, rash</td>
<td>15 months after neoplasm (concurred with relapse)</td>
<td>NSAIDs cyclophosphamide, 5-fluorouracil, methotrexate and prednisone</td>
<td>No response NSAIDs Complete remission with chemotherapy</td>
</tr>
<tr>
<td>Breast cancer&lt;sup&gt;3&lt;/sup&gt;</td>
<td>F</td>
<td>45</td>
<td>Polyarthralgia, fever</td>
<td>7 years after neoplasm (concurred with relapse)</td>
<td>prednisolone</td>
<td>Responded to moderate doses, could not be tapered &lt; 10 mg/day.</td>
</tr>
<tr>
<td>Breast cancer&lt;sup&gt;4&lt;/sup&gt;</td>
<td>F</td>
<td>52</td>
<td>fever, joint inflammation, pleuritis, and pericarditis</td>
<td>At the same time</td>
<td>Steroids Surgery</td>
<td>Not respond to steroids Complete remission after surgery</td>
</tr>
<tr>
<td>Breast cancer&lt;sup&gt;5&lt;/sup&gt;</td>
<td>F</td>
<td>49</td>
<td>Fever, rash, sore throat</td>
<td>At the same time</td>
<td>Steroid Chemotherapy-1 (Adriamycin, cyclophosphamide) Mastectomy Chemotherapy-2 (cyclophosphamide, 5-fluorouracil, tamoxifen)</td>
<td>Responded to steroids Complete remission with chemotherapy</td>
</tr>
<tr>
<td>Lymphoma&lt;sup&gt;6&lt;/sup&gt;</td>
<td>M</td>
<td>49</td>
<td>Fever, sore throat, pleuritic chest discomfort, polyarthritis</td>
<td>Symptoms were at the same time, but diagnosis of AOSD was made 1 year before.</td>
<td>NSAIDs Corticosteroids DMARDs (Metotrexate leflunomide, sulphasalazine, cyclosporine A) Chemotherapy (cyclophosphamide, vincristine, Adriamycin, prednisolone)</td>
<td>No response NSAIDs and DMARDs Responded to Corticosteroids but required high doses Complete remission after chemotherapy.</td>
</tr>
<tr>
<td>Lymphoma&lt;sup&gt;7&lt;/sup&gt;</td>
<td>M</td>
<td>50</td>
<td>fever, arthritis, myalgias.</td>
<td>12 months before neoplasm</td>
<td>Prednisone Cyclophosphamide</td>
<td>Responded to high dose of steroids; remission with maintenance treatment consisting low dose steroid and Cyclophosphamide.</td>
</tr>
</tbody>
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(Table continued on next page)
seem to be somewhat confusing. For example, Nakagawa and coworkers reported a case with chronic myelogenous leukemia that occurred 2 years after AOSD diagnosis. It is not clear, as the investigators suggested, whether it was a coincidence or a complication of cyclosporine A and cyclophosphamide treatment. Furthermore, the case reported by Bosch-Barrera and colleagues was also complicated. It was stated that the patient had developed fever, arthralgia, and rash, and laboratory examination revealed elevated C-reactive protein, pancytopenia, and hyperferritinemia during the chemotherapy. Although this patient had seemed to fulfill the Yamaguchi criteria, the diagnosis of hemophagocytic lymphohistiocytosis could not be excluded since the investigators have reported that the patient had pancytopenia. Kato and associates presented a similar patient with NK/T-cell lymphoma, firstly diagnosed as AOSD, and later hemophagocytic lymphohistiocytosis.

On the other hand, other cases with AOSD and malignancies suggest the overlook of an occult neoplasm. Despite the initial comprehensive investigation, some malignancies could not be detected. These cases emphasize one to consider the possibility of an underlying neoplasm, not only at initial evaluation, but also during the follow-up.

In conclusion, since most of the reported cases were concurred with primary neoplasm or relapse, and resolved after the treatment targeted to the underlying malignancies, AOSD seems to be a paraneoplastic syndrome. To control the symptoms, corticosteroids seem to be effective in patients with known underlying malignancies until the efficacy of anti-tumor therapy becomes evident. Furthermore, when a patient with a previous diagnosis of malignancy developed fever and hyperferritinemia, hemophagocytic lymphohistio-

Table 1 The Cases of Malignancy Associated Adult Onset Still’s Disease in Literature (continued)

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Sex</th>
<th>Age</th>
<th>Clinical features</th>
<th>Diagnosis Time</th>
<th>Treatment</th>
<th>Course of AOSD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic myelogenous leukemia</td>
<td>M</td>
<td>25</td>
<td>Fever, sore throat, rash</td>
<td>2 years before neoplasm</td>
<td>prednisolone, cyclosporine A, cyclophosphamide</td>
<td>Responded to pulse steroid and cyclophosphamide; remission continued with maintenance treatment consisting low dose steroid and cyclosporine A</td>
</tr>
<tr>
<td>Richter’s syndrome</td>
<td>F</td>
<td>53</td>
<td>intermittent fevers, rigors, night sweats, anorexia, weight loss, myalgia, arthralgia, rash.</td>
<td>7 months before neoplasm</td>
<td>cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) and rituximab</td>
<td>Complete remission</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>M</td>
<td>56</td>
<td>sore throat, fever, arthralgia</td>
<td>1 month after neoplasm</td>
<td>Nimesulide</td>
<td>Responded to nimesulide. Chemotherapy was continued. No relapse.</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>M</td>
<td>62</td>
<td>Fever, arthralgia, rash</td>
<td>5 months after neoplasm</td>
<td>Chemotherapy (Carboplatin, paclitaxel, erlotinib, pemetrexed, gemcitabine, prednisolone)</td>
<td>Occurred during chemotherapy regimen, responded to steroid</td>
</tr>
<tr>
<td>Lung Cancer</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>At the same time</td>
<td>Corticosteroids</td>
<td>NA</td>
</tr>
<tr>
<td>Papillary thyroid cancer</td>
<td>F</td>
<td>32</td>
<td>high spiking fevers, sore throat, and polyarthralgia</td>
<td>At the same time</td>
<td>Steroid total thyroidectomy, foll 131I thyroid ablation treatment</td>
<td>Responded to steroids. No recurrence after surgery and radionuclide treatment</td>
</tr>
<tr>
<td>Papillary thyroid cancer</td>
<td>M</td>
<td>68</td>
<td>Fever, arthralgia, myalgia, sore throat, macular eruption</td>
<td>At the same time</td>
<td>Steroids</td>
<td>Responded to high dose of steroids; could not be tapered &lt; 15 mg/day.</td>
</tr>
<tr>
<td>Esophageal cancer</td>
<td>M</td>
<td>77</td>
<td>fever, arthritis and rash</td>
<td>9 months before neoplasm</td>
<td>Steroids</td>
<td></td>
</tr>
</tbody>
</table>

NA, not available; M, male; F, female. References are respectively arranged from 1 to 15.
citosis should be considered in the differential diagnosis. Most importantly, the diagnosis of AOSD, as well as its differential diagnosis, should be made more cautiously, and it seems crucial to follow these patients more closely particularly within the first 2 years of presentation.

Disclosure Statement
None of the authors have a financial or proprietary interest in the subject matter or materials discussed, including, but not limited to, employment, consultancies, stock ownership, honoraria, and paid expert testimony.

References