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CASE REPORT

The first case of POEMS syndrome with synchronous breast cancer: What are the associated diagnostic challenges?

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Key Clinical Message

Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal gammopathy, Skin changes (POEMS) syndrome is a rare plasma cell disorder that causes a paraneoplastic syndrome. We report the first case of POEMS syndrome with synchronous breast cancer. The patient was at risk of being misdiagnosed with metastatic cancer, and it is important to emphasize that physical examinations provided vital diagnostic clues.

Keywords

Breast cancer, differential diagnosis, POEMS syndrome.

Introduction

Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal gammopathy, Skin changes (POEMS) syndrome causes the following clinical manifestations: (the initial letters of which form the word POEMS) as well as extravascular volume overload, erythrocytosis/thrombocytosis, osteosclerotic lesions, and elevated vascular endothelial growth factor (VEGF) levels [1]. Table 1 shows the diagnostic criteria for POEMS syndrome. The condition is diagnosed based on the presence of both polyradiculoneuropathy and a monoclonal plasma cell disorder, as well as at least one of the other three major criteria and at least one minor criterion. POEMS syndrome is often misdiagnosed because its symptoms mimic those of other disorders. In addition, it has a rapidly progressive course; therefore, early diagnosis is important. Pleural effusion, ascites, and/or cardiac effusion are the first symptoms to appear in more than half of patients with POEMS syndrome, and these conditions can become life-threatening in some cases [2].

Due to the abovementioned unique manifestations of POEMS syndrome, it can be difficult to achieve an early or accurate diagnosis in cases in which a patient with undiagnosed POEMS syndrome develops cancer. In other words, pleural effusion, ascites, lymphadenopathy, and bone lesions caused by POEMS syndrome might be misdiagnosed as cancer metastases if the preexisting POEMS syndrome is not detected. Herein, we present the first case report of POEMS syndrome with synchronous breast cancer and describe potential diagnostic problems associated with such cases.

Case history/examination

A 65-year-old female with a chief complaint of coxalgia, which had lasted for 2 years, presented to a nearby hospital. A computed tomography (CT) scan showed multiple sclerotic bone lesions, which were suggestive of an occult

Table 1. The criteria for POEMS syndrome.

Major criteria (both required)	1. Polyneuropathy (typically demyelinating)
	2. Monoclonal gammopathy
Other major criteria (1 required)	3. Castleman's disease
	4. Sclerotic bone lesions
	5. Elevated VEGF levels
Minor criteria (1 required)	6. Organomegaly (splenomegaly, hepatomegaly, or lymphadenopathy)
	7. Extravascular volume overload (edema, pleural effusion, or ascites)
	8. Endocrinopathy
	9. Skin changes (e.g., hyperpigmentation, hemangioma, etc.)
	10. Papilledema
	11. Thrombocytosis or polycythemia
Other symptoms and signs	Clubbing, weight loss, hyperhidrosis, pulmonary hypertension/restrictive lung disease, thrombotic diatheses, diarrhea, low vitamin B12 values

VEGF: vascular epithelial growth factor.

primary tumor and multiple bone metastases. Despite extensive testing for 3 months, no final diagnosis was made so the patient was referred to our hospital for a second opinion. By that time, she had developed further symptoms; that is, a prolonged bloating sensation and visible abdominal distension, which had lasted for a month. She received a thorough examination at our hospital's internal medicine department, including various blood tests; imaging examinations, such as CT and mammography; upper and lower endoscopy; and cytoscreening (a biochemical examination) of her ascites. The differential diagnosis process particularly focused on autoimmune connective tissue disorders in addition to a further examination for occult primary cancer. The patient's laboratory data were indicative of anemia, thrombocytopenia, low serum albumin levels, kidney dysfunction, and subclinical hypothyroidism, but no autoantibodies associated with autoimmune connective tissue disorders were detected (Table 2A–B). A CT scan showed a small to moderate amount of pleural effusion, a large amount of ascites, enlargement of both axillary lymph nodes, and multiple sclerotic bone lesions, but did not detect any tumors of the parenchymal organs or lymphadenopathy (Fig. 1A–C). Diagnostic aspiration indicated that the patient's ascites (Table 3) was transudative, but not malignant. A right-sided mammography showed a cluster of pleomorphic microcalcifications (Fig. 2A). In agreement with this lesion, a breast ultrasound scan detected a hypoechoic solid tumor (size: ~1 cm) containing internal echogenic spots with interruption of both the anterior and posterior borders of the mammary gland (Fig. 2B). Therefore, an ultrasound-guided needle biopsy was performed, leading to a histopathological diagnosis of hormone receptor-positive invasive ductal carcinoma without human epidermal growth factor receptor type 2 (HER2) protein overexpression (Fig. 3). Although the diagnostic aspiration did not provide conclusive evidence of malignant effusion, after reflecting on the patient's pathological characteristics, the physicians made a final diagnosis of stage IV/metastatic breast cancer with metastases involving the pleural cavity, peritoneal cavity, lymph nodes, and bone. The patient began receiving tamoxifen-based hormonal therapy because chemotherapy was deemed inappropriate due to coexisting renal impairment. 1 month later, it became difficult for the patient to live at home because her massive ascites induced a bloating sensation accompanied by pain, shortness of breath, a diminished appetite,

Table 2. Laboratory findings.(A) Abnormal laboratory data obtained on admission and the changes in these parameters after chemotherapy treatment. (B) A list of the autoantibodies associated with autoimmune connective tissue disorders that were tested for on admission.

	On admission	After two courses of chemotherapy
(A)		
White blood cells (/μL)	3300	5300
Red blood cells (10^4/μL)	274	267
Hemoglobin (g/dL)	8.1	8.4
Platelets (10^3/μL)	115	126
Total protein (g/dL)	5.7	6.6
Albumin (g/dL)	2.7	4.0
BUN (mg/dL)	74.2	33.6
Creatinine (mg/dL)	2.2	1.5
IgG (mg/dL)	1681	1353
IgA (mg/dL)	228	171
IgM (mg/dL)	88	109
TSH (mIU/mL)	8.495	2.581
FT3 (pg/mL)	0.57	1.36
FT4 (ng/mL)	5.03	0.88

(B)	
Autoimmune antibody (titer)	1:<40
Anti-DNA antibody (IU/mL)	<2.0
Lupus-anticoagulant (sec)	1.0
Anticardiolipin antibody (U/mL)	<1.2
Anti-RNP antibody	not detected
Anti-Sm antibody	not detected
Anti-SS-A antibody	not detected
p-ANCA (U/mL)	<1.0
c-ANCA (U/mL)	<1.0
Anti-TPO antibody (IU/mL)	8.0

BUN: blood urea nitrogen, TSH: thyroid-stimulating hormone, FT3: free triiodothyronine, FT4: free thyroxine, RNP: ribonucleoprotein, SS-A: Sjögren's syndrome-related antigen A, ANCA: antineutrophil cytoplasmic antibodies, TPO: thyroid peroxidase.

[Correction added on 21 March 2016 after first online publication: The units in tables 2 and 3 were incorrect and have been updated in this version]

nausea, severe fatigue, and edema of the lower extremities. Therefore, she was admitted to our surgical ward in order to undergo peritoneal port-catheter placement to manage her refractory ascites.

Differential diagnosis, examinations, and treatment

The surgeon who performed the physical examination on admission (the lead author of this article) noted that the patient had several characteristic physical findings: clubbing and hyperpigmentation of the fingers (Fig. 4A); skin hyperpigmentation on her back together with angiomas (Fig. 4B); and polyneuropathy, for example, numbness in both fingers, an inability to sense vibrations in both upper extremities, muscle weakness, and diminished deep tendon reflexes. The detection of these characteristic physical findings triggered a fundamental review of the previous diagnosis, which required us to reexamine whether the patient's breast cancer had played a causal role in the development of her pleural effusion, ascites, axillary lymphadenopathy, and sclerotic bone lesions. When we considered all of the patient's findings (other than the breast cancer) in a comprehensive manner, the differential diagnoses were divided into the following three categories: [1] hematological disorders, such as multiple myeloma, POEMS syndrome, monoclonal gammopathy of undetermined significance, Waldenstrom's macroglobulinemia, cryoglobulinemia, and amyloidosis; [2] immune-mediated peripheral neuropathies, such as chronic inflammatory demyelinating polyneuropathy; and [3] autoimmune connective tissue disorders, such as scleroderma. However, autoimmune connective tissue disorders had already been ruled out, as mentioned above. On the other hand, the patient's physical findings; that is, the skin and neurological manifestations, represented valuable clues and led to an in-depth examination for POEMS syndrome.

Table 3. Laboratory chemical analysis of the patient's ascites. The results indicated that the ascites was transudative, but not malignant.

Gradient	1.024
Rivalta reaction	negative
Protein (g/dL)	3.3
Albumin (g/dL)	1.8
Glucose (mg/dL)	111
Lactate dehydrogenase (U/L)	55
Total cell count (/μL)	496
Mononuclear cells (/μL)	487
Polynuclear cells (/μL)	9

[Correction added on 21 March 2016 after first online publication: The units in tables 2 and 3 were incorrect and have been updated in this version]

To examine whether the patient met the major criteria for POEMS syndrome (Table 1), we performed an iliac crest bone marrow biopsy, a test for M-protein, and a nerve conduction velocity (NCV) test. The bone marrow biopsy showed normal cellularity and did not detect any bone marrow plasma cell involvement, which excluded multiple myeloma. However, IgG-λ monoclonal gammopathy was detected (Fig. 5), and the NCV test demonstrated both demyelination and axonopathy in the right upper extremities (Table 4), which were considered to be

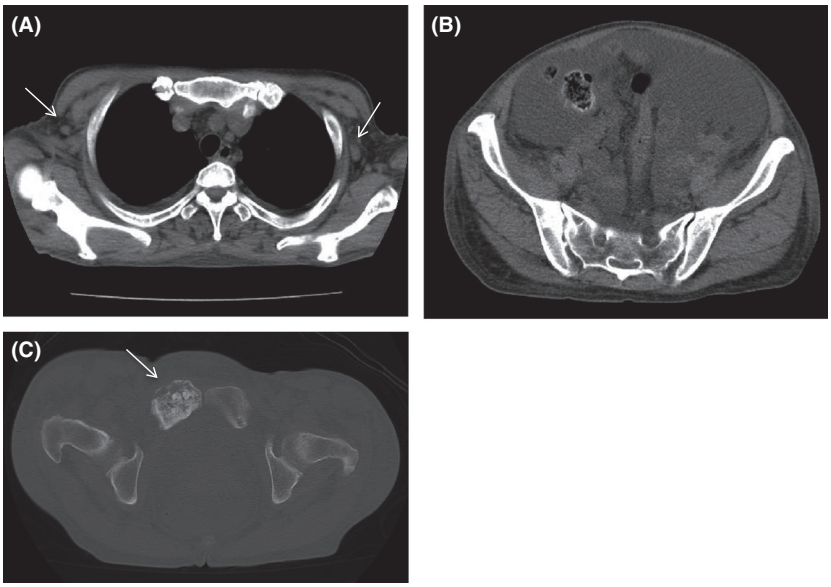

Figure 1. CT scan obtained on admission. The scan showed (A). bilateral axillary lymph node enlargement (white arrows), (B). a large amount of ascites, and (C). a bone sclerotic lesion in the pubic symphysis (white arrow).

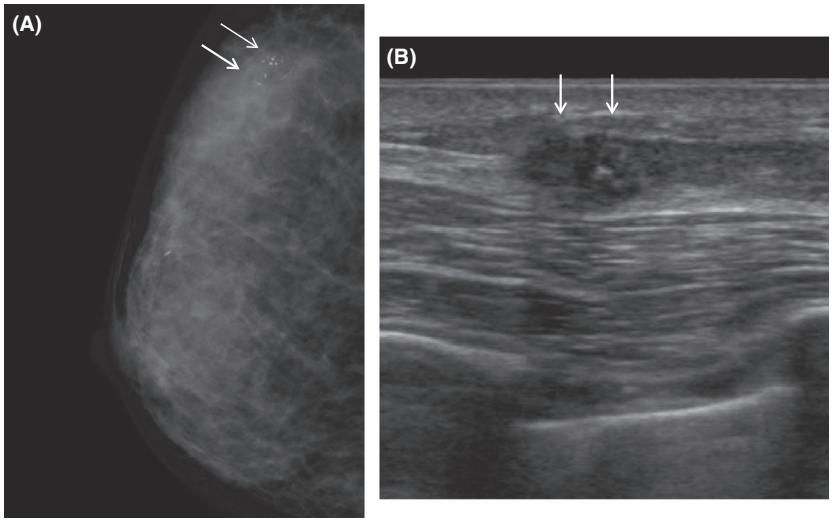

Figure 2. Imaging studies of the right breast. (A). A right-sided mammography showed a cluster of pleomorphic microcalcifications (white arrows). (B). A breast ultrasound detected a hypoechoic solid tumor (size: ~1 cm) containing internal echogenic spots with interruption of both anterior and posterior border of the mammary gland (white arrows).

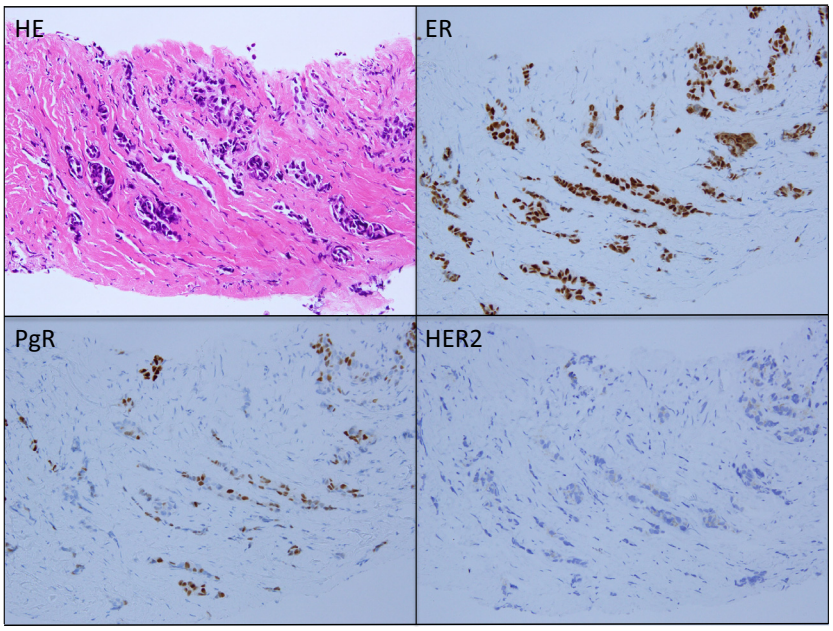

Figure 3. Histopathological examinations of the right breast An ultrasound-guided needle biopsy detected hormone receptor-positive invasive ductal carcinoma without human epidermal growth factor receptor type 2 (HER2) protein overexpression. HE: hematoxylin-eosin, ER: estrogen receptor, PgR: progesterone receptor

comorbidities of the patient's peripheral polyneuropathy. Thereby, the diagnostic criteria for POEMS syndrome were fulfilled because one element of the other three major criteria (sclerotic bone lesions) and three of the minor criteria (lymphadenopathy, extravascular volume overloading, and skin changes) had already been met. In addition, we obtained further strong evidence to support this diagnosis; that is, a markedly raised VEGF level; the patient's plasma and serum VEGF levels were 555 pg/mL and 1530 pg/mL, respectively. It has been reported that a plasma VEGF level of 200 pg/mL exhibits 95% specificity and 68% sensitivity for diagnosing POEMS syndrome [3]. According to the Japanese diagnostic criteria for POEMS syndrome issued by the Japan Intractable Diseases Information Center, a significantly elevated VEGF level is defined as a serum level of >1000 ng/mL [4]. Therefore,

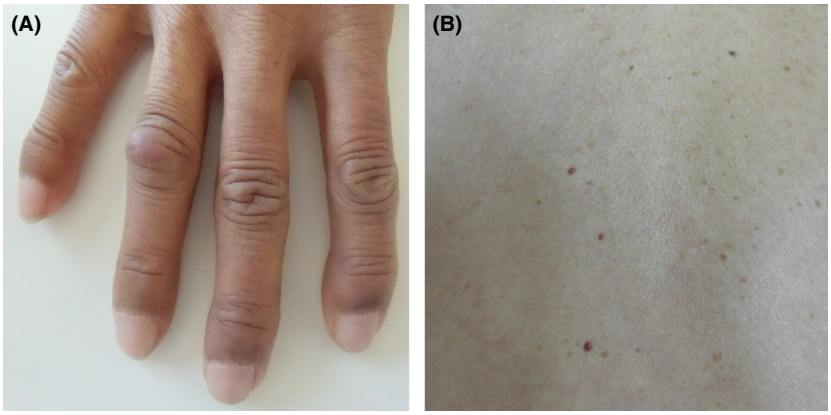

Figure 4. Skin changes (A). Finger clubbing with hyperpigmentation (B) Hyperpigmentation of the back with angiomas

we were able to make a definitive diagnosis of POEMS syndrome in this rare case, which also involved synchronous breast cancer.

Immediately after the final diagnosis, the patient began receiving chemotherapy based on a regimen for multiple myeloma (1.3 mg/m^2 bortezomib, SC, on days 1, 8, 22, and 29 of each cycle and 20 mg dexamethasone, PO, on days 1, 2, 8, 9, 22, 23, 29, and 30 of each cycle; each cycle lasted 6 weeks) [5] as her condition was becoming increasingly life-threatening.

Outcomes and follow-up

After two courses of chemotherapy, the patient's pleural effusion and ascites had almost disappeared, and her plasma and serum VEGF levels fell significantly to 47 pg/mL and 266 pg/mL, respectively; that is, below the diagnostic cut-off values of 200 pg/mL and 1000 pg/mL, respectively, indicating that these symptoms had been caused not by cancerous dissemination, but by POEMS syndrome. With the decreasing extravascular volume overload, her circulating plasma volume increased, leading to an improvement in her kidney function (see Table 2A), for example, her estimated glomerular filtration rate improved from 18 mL/min to 28 mL/min. Thus, the patient's condition had improved markedly, and she was well enough to undergo a radical operation for breast cancer under general anesthesia.

The patient underwent total mastectomy and complete axillary node dissection for right breast cancer. A histopathological examination of the resected specimens detected a 10 × 5 mm-sized invasive ductal carcinoma with no lymph node involvement (0/19). When investigating the dissected axillary lymph nodes for POEMS syndrome, none of the following histopathological features of Castleman's disease were detected: hyaline vascular, plasmacytic, or mixed lymph node features. Her breast cancer subtype was diagnosed as luminal A [6]. Accordingly, adjuvant endocrine therapy (5 years' tamoxifen treatment) was considered sufficient.

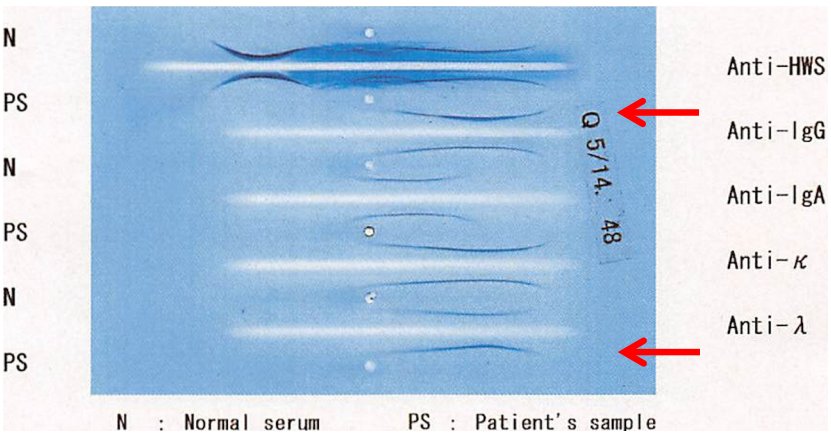

Figure 5. Immunoelectrophoresis The patient exhibited monoclonal gammopathy of IgG-λ (red arrows).

Table 4. A NCV study of the patient's right side.

		Distal latency (msec)	Amplitude (mV)	NCV (m/sec)
Median	motor	7.35 (3.0–3.8)	7.01 (5.3–11.1)	28.5 (53.8–61.4)
	sensory	unmeasurable		
Ulnar	motor	6.75 (3.3–2.9)	4.28 (5.6–9.2)	34.0 (53.4–62.6)
	sensory		22.0 (13.5–34.1)	33.7 (51.0–61.6)
Tibial	motor	unmeasurable		
Peroneal	motor	unmeasurable		
Sural	sensory	unmeasurable		

NCV, nerve conduction velocity.

As a reference, normal values are shown in parentheses. [22] This test detected mixed neuropathy in the median motor nerve and ulnar motor nerve (a long latency, low amplitude, and low NCV), and axonal neuropathy in the right ulnar sensory nerve (a low NCV). The NCV of the median sensory nerve, tibial motor nerve, peroneal motor nerve, and sural sensory nerve were unmeasurable.

After receiving several more cycles of the same chemotherapy regimen, the patient is scheduled to receive an autologous stem cell transplant in the near future, which is expected to result in a substantial improvement in her neuropathy [7] [8].

Discussion

POEMS syndrome was first reported by Crow in 1956 [9] and was subsequently described by Fukase in 1969 [10]. The acronym POEMS was coined by Bardwick in 1980 [11] and stands for the five main features of the disease; that is, polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes. The syndrome was also referred to as Crow–Fukase syndrome by Nakanishi in 1984 based on a Japanese study of 102 cases [12], and this name is more widely known in Japan than POEMS syndrome.

Although the pathophysiology of POEMS syndrome is poorly understood, the production of various inflammatory cytokines, such as interleukins (IL-1 and IL-6) and VEGF, by abnormal plasma cells is postulated to play a direct causal role in various symptoms of the condition [13, 14]. In particular, VEGF levels exhibit the strongest correlations with disease activity in POEMS syndrome [3,15]. Plasma and serum VEGF levels of 200 pg/mL and 1,000 pg/mL, respectively, are considered to be diagnostic cut-off values for POEMS syndrome. Elevated VEGF levels are postulated to be involved in the pathogenesis of enhanced vascular permeability, increased endoneurial pressure, and the deposition of plasma cell-derived material [14, 16, 17], which eventually cause a variety of symptoms, including extravascular volume overloading (edema, pleural effusion, and/or ascites), polyneuropathy (demyelination), sclerotic bone lesions, and skin changes [18, 19]. However, the mixed results seen with anti-VEGF therapy indicate that VEGF might not be the driver of the clinical manifestations of POEMS syndrome [20]. Further studies of this issue are required.

To the best of our knowledge (based on a search of the PubMed database), this is the first case report about a case of POEMS syndrome with synchronous breast cancer. Using "POEMS syndrome" and "synchronous cancer" as search keywords, we did not find any relevant articles (accessed Oct 19, 2015). At present, there is no evidence that certain types of cancer are strongly associated with POEMS syndrome. Thus, it is likely that the current patient developed POEMS syndrome and breast cancer synchronously by chance.

The following three major factors might help to explain the diagnostic difficulties encountered in the present case. First, POEMS syndrome is a rare disease; its prevalence rate was reported to be 0.3 per 100,000 in Japan [17]. However, there is another fact that some patients with POEMS syndrome are first diagnosed at autopsy or go undiagnosed unless properly autopsied because of diagnostic challenges specific to the syndrome [21], which makes the actual prevalence rate unclear. Second, many of the signs and symptoms of POEMS syndrome mimic those of other disorders, leading to confusion and difficulties during the diagnostic process. Especially when being diagnosed with a certain type of cancer before the detection of preexisting POEMS syndrome, pleural effusion, ascites, lymphadenopathy, and bone lesions might be considered to be carcinomatous in origin. The risk of such mistakes is probably higher in cases involving a metastasis-prone cancer, for example, breast cancer. Third, clinicians have recently appeared to rely excessively on laboratory findings and/or imaging studies during the diagnostic process. This trend downplays the significance of physical examinations. The present case should act as a warning against this unfavorable trend and could yield a bitter but helpful lesson that, "the more complex a disease is, the more important a physical examination tends to be".

Conflict of interest

None declared.

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