A 69-year-old woman presented to the general internal medicine clinic with complaints of headache, fever, and rash. Throbbing pain at the left temporal region and left posterior auricular area had begun two months ago. Twenty days before her visit to our clinic she had a fever of 38℃, and her primary care doctor prescribed clarithromycin. The fever persisted for ten days, and clarithromycin was changed to levofloxacin. Her fever subsided after three days and levofloxacin was discontinued. Low-grade fever was persistent. Three days before her visit to our clinic, she found non-itchy red rashes on her right arm. She visited another primary care doctor and a plain abdominal CT was performed with unremarkable findings. Just before her visit to our clinic, she had left scapula and left breast pain in addition to pain in the left temporal region and left posterior auricular area. During the past six months, she had body weight loss of 3 kg, but she did not have general malaise, shaking chills, night sweats, nausea, vomiting, abdominal pain, diarrhea, bloody diarrhea, nor jaw claudication.

Fever is a non-specific symptom and a diagnosis cannot be made without paying attention to other clues, that is, associated symptoms. A patient with fever and headache could have viral infection syndrome, meningitis, sinusitis or temporal arteritis (TA). The patient should be checked for neck stiffness and jolt accentuation, which would suggest meningitis. If she did have meningitis, her chronic course suggested aseptic meningitis such as tuberculosis meningitis rather than bacterial meningitis. The patient should be examined for face pain or pressure, congestion, nasal discharge or post-nasal drip, and sinus percussion tenderness, which would suggest sinusitis.

Jaw claudication is only seen in 50% of temporal arteritis cases. By contrast, physical findings of swelling, tenderness, and pulse defect in the temporal artery are highly specific for TA. TA cannot be ruled out if a patient does not have jaw claudication. But the likelihood of TA becomes high if a patient has these findings. Rash has low specificity. Rash is seen in patients with viral infection, drug eruption, vasculitis, and so on. However, if a rash is palpable purpura, it is helpful to diagnose vasculitis. Unfortunately, potential diagnoses mentioned here cannot explain the left scapula and left breast pain.
She did not have a past history of hypertension, diabetes mellitus, or dyslipidemia. She had a history of herpes zoster, hemorrhoid, duodenal ulcer, and total hysterectomy due to endometriosis. She did not take any medications or supplements. Her family history included no cancer or autoimmune disease.

Her past history and background were not significant.

On physical examination, the patient appeared well. Her blood pressure was 104/64 mmHg, pulse was 83 bpm, respiratory rate was 14/min, and body temperature was 35.9℃. Her height was 156 cm and weight was 40.4 kg. Bulbar conjunctivae were not icteric or anemic. Jugular venous pressure was normal. There was no tenderness over the maxillary or frontal sinuses or temporal arteries, but there was tenderness over the left temporal region and left posterior auricular area. Neck stiffness and jolt accentuation were not seen. Any superficial lymph nodes were not palpable. Cardiac examination revealed a regular rate and rhythm, with a holosystolic murmur at the apex. There was tenderness over the left scapula and left breast. Abdominal examination was unremarkable. Rashes of 2 mm in diameter, red-brown, and impalpable were scattered across her limbs, but Janeway lesions and Osler’s nodes were not seen.

Her vital signs were stable, suggesting no acute deteriorating condition. There was no strong evidence to suspect meningitis, sinusitis or TA from the physical examination. The patient had a systolic murmur and, although she did not have Janeway lesions or Osler’s nodes, infectious endocarditis needed consideration. Two-set and more blood cultures needed to be drawn, as well. The presence of rash is nonspecific and not helpful for diagnosis, but an impalpable characteristic reduces the likelihood of vasculitis.

Her white cell count was 5100/mm³ with 24% lymphocytes, 9.3% monocytes, 63.7% neutrophils, 2.8% eosinophils, and 0.2% basophils. Her hemoglobin was 11.2 g/dL, and the platelet count was 278,000/mm³. Other laboratory tests revealed the following values: total protein, 6.35 g/dL; albumin, 3.14 g/dL; creatine phosphokinase, 23 U/L; aspartate aminotransferase, 20 U/L; alanine aminotransferase, 16 U/L; lactate dehydrogenase, 448 U/L; alkaline phosphatase, 290 U/L; amylase, 41 U/L; creatinine, 0.62 mg/dL; blood urea nitrogen, 14.8 mg/dL; glucose, 101 mg/dL; sodium, 137 mEq/L; potassium, 4.4 mEq/L; chloride, 99 mEq/L; total bilirubin, 0.34 mg/dL; and, C-reactive protein, 4.52 mg/dL. Urinalysis was negative for casts, protein and occult blood. Chest X-ray was normal.

Initial evaluation by laboratory tests revealed only the existence of inflammation. High lactate dehydrogenase, with normal value being about 107 to 245, can result from lymphoma, hemolytic anemia, myocardial infarction, and others causes but is not so specific. The presence of inflammatory reaction together with fever and generalized pain suggests vasculitis, especially small and medium vessel vasculitis. Therefore, p-ANCA and c-ANCA should be checked. The possibility of drug eruption, drug fever, and viral infection still remained.

Blood cultures and p/c-ANCA were drawn, which all came out negative. Loxoprofen, a non-steroidal anti-inflammatory drug (NSAID), was prescribed. Six days after the first visit, the pain in the left temporal and left posterior auricular area disappeared, but tenderness of the left scapula and breast remained. Low-grade fever persisted.

Negative blood cultures and lack of skin stigma reduce the likelihood of infectious endocarditis. The likelihood of TA is also low because of the lack of tenderness of the temporal artery. Negative urinalysis, lack of purpura, and negative p-ANCA reduce the possibility of microscopic polyangiitis. Lack of asthma, eosinophilia, and pulmonary infiltrative shadow reduces the possibility of Churg-Strauss syndrome.

Lack of pulmonary and kidney involvement and negative c-ANCA reduce the possibility of Wegener granulomatosis.
Eight days after the first visit, she came back to the clinic, complaining of increasing fatigue, anorexia and watery diarrhea. She was suspected of having adverse effects of loxoprofen, and lansoprazole (a proton pomp inhibitor) was administered. Four days later, new pain in the right femoral region appeared. The watery diarrhea was resolved, but constipation began. She felt numbness and the sensation of food spilling from the right angle of her mouth. Fatigue, anorexia, dry mouth, nausea, vomiting, constipation and pain in multiple regions became exacerbated. She was hospitalized for further evaluation.

There are several steps to make a diagnosis in this complicated case. The first step is to think of differential diagnoses for fever of unknown origin (FUO). The criteria for FUO advocated by Petersdorf include: a) fever higher than 38.3℃ on several occasions; b) duration of fever for at least three weeks; and, c) uncertain diagnosis after three days of study in hospital or outpatient studies performed three times. This patient fulfilled the criteria. Three major categories of FUO are infection, malignancy and connective tissue disease. Infectious endocarditis (IE), tuberculosis (Tb), renal cell carcinoma (RCC), hepatocellular carcinoma (HCC), malignant lymphoma, dermatomyositis, polymyositis, rheumatoid arthritis, and vasculitis syndrome are evoked for this patient from the three categories.

1) As stated above, IE had already been ruled out. Abdominal CT performed by a previous doctor showed no evidence of RCC and HCC, but malignant lymphoma could not be ruled out. The possibility of connective tissue diseases other than polyarteritisnodosa is low. The second step is narrowing the differential diagnoses in terms of the problem list. In this case, the problem list included fever, general malaise, anorexia, dry mouth, constipation, nausea, vomiting, weight loss, mouth numbness, food spilling, systemic pain with point tenderness, and chronic inflammation. If a disease name suddenly comes to mind while looking at this problem list, it is a likely diagnosis. This process is called snap diagnosis, or pattern recognition. Sometimes specific or high-yield problems help to narrow the differential diagnoses, such as pancytopenia or jaundice. Unfortunately, the problems are so nonspecific that they do not help. Mouth numbness and food spilling might be symptoms of facial nerve palsy. But even nerve palsy is peripheral because this patient do not have evidence of other cranial nerve symptoms. It seems unhelpful for diagnosis. Instead, paying attention to combinations of problems is thought to be help. A combination of malaise, anorexia, vomiting, dry mouth and constipation suggests hypercalcemia. Then, a constellation of hypercalcemia and systemic pain suggests cancer with bone metastasis. This diagnostic hypothesis could also explain her fever. Based on this idea, the different primary diagnoses include cancer with bone metastasis, malignant lymphoma, tuberculosis and polyarteritisnodosa. Skull X-ray and head plain CT should be performed to check for osteolytic lesions. The serum level of calcium also should be checked.

Simple skull x-ray (Figure 1) showed multiple lytic bone lesions. Head CT (Figure 2) confirmed lesions with invasion of soft-tissue-density mass. The serum calcium level was 16.5 mg/dL. Normal saline, furosemide, calcitonin and zoledronic acid hydrate were administered for hypercalcemia.

The presence of hypercalcemia and multiple lytic bone lesions with tumor was confirmed. Bone metastasis may occur in carcinoma of the lung, breast, kidney, prostate, or thyroid and malignant melanoma. Multiple myeloma is a common cause of skull osteolytic lesion. Quantitation of serum IgG, IgA and IgM, immunoelectrophoretic study, and testing for Bence Jones protein (BJP) in the urine should be performed. In addition, biopsy of head lesions is needed.

Serum immunoglobulins were not elevated (IgG 1118 mg/dL; IgA 175 mg/dL; IgM 175 mg/dL). Immunoelectrophoresis showed no monoclonal gammopathy, and urinary BJP was negative. The serum levels of PTH-rP and 1,25-dihydroxyvitamin D were 2 pmol/l and 10.2 pg/ml, respectively. The intact PTH level was 2 pg/ml.
Hematoxylin and eosin staining of a biopsy specimen of a head lesion (Figure 3a) showed a mixture of large and small cells. The tumor cells strongly expressed the B-cell antigen CD20 (Figure 3b) and were negative for the T-cell antigen CD3. Diffuse large B-cell lymphoma (DLBCL) with multiple bone invasion was diagnosed.

Gallium scan (Figure 4) revealed multiple abnormal uptake sites in the skull, bilateral shoulder joints, rib, vertebrae, pelvis and limb bones. Normal PTH-rP and 1,25(OH)₂D levels with reduced intact PTH level, and multiple lytic bone lesions suggested local osteolytic hypercalcemia (LOH). The patient was treated with chemotherapy of the R-CHOP regimen, which consisted of rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine (oncovin), and prednisone. Fatigue, dry mouth, nausea and constipation resolved accompanied by improvement of hypercalcemia. After several courses of the treatment, she achieved remission.

**DISCUSSION**

Symptoms of hypercalcemia include fatigue, weak...
ness, dry mouth, anorexia, constipation, polydipsia, polyuria, and mental confusion. These symptoms are nonspecific and the recognition of hypercalcemia is difficult unless the physician has a high degree of suspicion.

The major causes of hypercalcemia are primary hyperparathyroidism and malignancy. These two etiologies account for 80% of hypercalcemia cases. The proportion of malignancy-related cases is increasing among hospitalized patients. Other rare causes include particular drugs and granulomatous disease.

Hypercalcemia is relatively common in patients with cancer, occurring in approximately 20 to 30 percent of cancer cases. In malignancy-related hypercalcemia, both bone resorption and release of calcium from bone are increased. There are four major mechanisms: local osteolytic metastasis (LOH); tumor secretion of PTH-rP; tumor secretion of 1,25(OH)2D; and, tumor secretion of parathyroid hormone. The hypercalcemia caused by PTH-rP is called humoral hypercalcemia of malignancy (HHM). HHM accounts for approximately 80% of malignancy-related hypercalcemia cases, and LOH accounts for approximately 20% of cases. The other mechanisms comprise less than 1% of cases. HHM is common among squamous cell carcinoma cases, but is seen in all types of malignant lymphoma. LOH is most common among breast cancers and multiple myelomas, and less common among malignant lymphomas. 1,25(OH)2D secretion is occasionally seen in Hodgkin and non-Hodgkin lymphoma with hypercalcemia. Regarding malignant lymphoma, hypercalcemia is observed in 15% of cases, and all types of mechanisms can exist.

The present patient had three clinical conditions: paraneoplastic fever, pain of bone metastasis, and symptoms of hypercalcemia. The symptoms appeared at various times and the whole feature of the disease was very complicated. In this case, grouping nonspecific symptoms such as malaise, anorexia, dry mouth, constipation and vomiting, led to a suspected diagnosis. Furthermore, the combination of hypercalcemia, fever and systemic pain led to a diagnostic hypothesis of cancer with bone metastasis and paraneoplastic fever, which could explain all features of this patient.

As indicated in this case, it is helpful to group problems when they are too complex to make a rapid diagnosis.

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Figure 4. Gallium scintigraphy
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