Authors' Disclosures of Potential Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

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Bone marrow metastasis of small cell lung carcinoma with spontaneous tumor lysis syndrome without hepatic metastasis at diagnosis: first case report in Korea and review of literature

TO THE EDITOR: Tumor lysis syndrome (TLS) is a severe metabolic and electrolytic disturbance caused by rapid lysis of neoplastic cells, and resulting in various end-organ damages. TLS is frequently encountered in tumors with high cell turnover and growth rates such as hematologic malignancies including acute leukemias, Burkitt lymphoma, and high-grade lymphomas, and is commonly observed in these patients after administration of induction chemotherapy, radiotherapy, or cytolytic antibody therapy [1, 2]. TLS unrelated to therapy is defined as spontaneous TLS (STLS), which can be observed in patients with the aforementioned hematologic malignancies, but the incidence of STLS is lower than that of TLS associated with prior therapy [3, 4]. TLS is also rarely encountered in patients with solid cancers. STLS in small cell lung carcinoma (SCLC) was first reported in 2008, and since then, only five other cases have been reported up to present time [3-7]. We report here a case of STLS associated with bone marrow (BM) metastatic SCLC without hepatic metastasis at diagnosis, and to our best knowledge, this is the first case report of STLS with BM metastatic SCLC in Korea.

A 71-year-old man visited our institution in January 2019 with increased nodule size in the right lower lobe (RLL) of the lungs. The RLL nodule was initially found five years prior, but its size had decreased at follow-up and it was regarded as an inflammatory nodule. Computed tomography (CT) showed the development of ill-defined ground-glass opacities in the right upper lobe of the lungs accompanied by multiple lymphadenopathies in the right supraclavicular, prevascular, upper paratracheal, both lower paratracheal, subcarinal, and left paraesophageal lymph nodes, but evidence of hepatic or renal metastasis of solid cancer was not found. The hemogram and peripheral blood smear results of the patient at the first visit were as follows: white blood cells, $6.09 \times 10^9/L$; hemoglobin, 10.3 g/dL; and platelets, $7.0 \times 10^9/L$. The complete blood cell differential count results of the patient at the first visit were as follows: metamyelocytes, 3%; band neutrophils, 12%; segmented neutrophils, 44%; lymphocytes, 33%; monocytes, 7%; basophils, 1%; and the presence of nucleated red blood cells (nRBCs) with a frequency of 5 nRBCs/100 white blood cells. At initial workup, the patient showed increased inorganic phosphate (6.9 mg/dL, reference range, 2.9-4.3), uric acid (11.9 mg/dL, reference range, 2.1-7.4), fibrinogen degradation product (81.99 $\mu g/mL$, reference range, <5.00), D-dimer (6.53 $\mu g/mL$, reference range, <0.50), lactate dehydrogenase (3922 IU/L, reference range, 106-230), and creatinine (1.77 mg/dL, reference range, 0.60-1.50) levels and prolonged prothrombin time (13.3 s, reference range, 9.3-13.2). The patient also showed normal potassium (4.10 mM/L, reference range, 3.50-5.30) and calcium (8.6 mg/dL, reference range, 7.8-10.0) levels and a decreased fibrinogen (146.0 mg/dL, reference range, 200.0-400.0) level. At the previous visit to another hospital 2 months prior, the patient showed normal uric acid (3.7 mg/dL, reference range, 2.5-8.3) and creatinine (0.78 mg/dL, reference range, 0.6-1.2) levels. For the pathologic diagnosis, endobronchoscopic ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) and liquid-based aspiration cytology from the lymph nodes, BM aspiration, and biopsy were performed.

The BM aspiration showed hypocellular marrow due to dilution by peripheral blood with infiltration of small to medium-sized neoplastic cells at a frequency of 56.0%, which showed deeply stained nuclei, finely dispersed nuclear chromatin without distinct nucleoli, scanty amount of cytoplasm, and frequent nuclear moulding defined as conformity of adjacent cell nuclei to one another (Fig. 1A-C). BM biopsy showed hypercellular marrow (cellularity 90%) with proliferation of neoplastic cells in a diffuse and patched pattern accompanied with frequent nuclear moulding (Fig. 1D-F). Subsequently performed immunohistochemical (IHC) staining in BM biopsy sections showed the presence of neoplastic cells with positivity for cluster of differentiation (CD)56 (Fig. 1G), cytokeratin (Fig. 1H), and chromogranin (Fig. 1I). Both CD3 and CD20 IHC stains showed the presence of a few reactive T and B lymphocytes, without evidence of neoplastic lymphoid cell infiltrations. Based

Fig. 1. Bone marrow aspiration, biopsy, and immunohistochemical stain results of the patient. The bone marrow aspiration (A–C) showed hypocellular marrow due to dilution by peripheral blood with increased infiltration of small to medium-sized neoplastic cells, which showed deeply stained nuclei, finely dispersed nuclear chromatin without distinct nucleoli, scanty amount of cytoplasm, and frequent nuclear moulding defined as conformity of adjacent cell nuclei to one another (Wright stain, $\times 400$). The bone marrow biopsy (D–F) showed hypercellular marrow with proliferation of neoplastic cells in a diffuse and patched pattern accompanied by frequent nuclear moulding (Hematoxylin and Eosin stains, $\times 200$ in D, $\times 200$ in E, $\times 400$ in F). Subsequently performed immunohistochemical stains showed the presence of neoplastic cells with positivity for CD56 (G, $\times 400$), cytokeratin (H, $\times 400$), and chromogranin (I, $\times 400$).

on these results, the diagnosis of BM metastasis of SCLC was made. Liquid-based aspiration cytology showed the presence of neoplastic cells favoring metastatic SCLC, and lymph node specimens obtained from EBUS-TBNA also showed positivity for CD56, cytokeratin, and chromogranin IHC stains, which corresponded with the IHC staining results of the BM biopsy sections. Based on these results, the pathologic diagnosis of SCLC was confirmed. Since the patient showed hyperuricemia (11.9 mg/dL) and hyperphosphatemia (6.9 mg/dL), and these results fulfilled the diagnostic criteria for laboratory TLS [1, 8], which requires two or more of four metabolic abnormalities (defined as hyperuricemia ≥ 8.0 mg/dL or $>25\%$ increase from baseline, hyperkalemia ≥ 6.0 mM/L or $>25\%$ increase from baseline, hyperphosphatemia ≥ 4.49 mg/dL or $>25\%$ increase from baseline, and hypocalcemia ≤ 7.0 mg/dL or $>25\%$ decrease from baseline) within 3 days before or up to 7 days after induction of therapy, our patient was finally diagnosed with BM metastatic SCLC with STLS; he also showed a typical laboratory finding of disseminated intravascular coagulation. At present, our patient is awaiting palliative chemotherapy for SCLC.

Although TLS is frequently observed in hematologic malignancies, such as acute leukemias or high-grade lymphomas, the incidence of TLS associated with solid tumors re-

mains relatively low because they have such a low proliferative index, and a few case reports of TLS associated with solid cancer support this speculation [3, 9]. In addition, STLS in solid tumors is an extremely rare situation and has been reported in only a few cases [3]. Although only a few cases of STLS in SCLC have been reported previously [3–7], SCLC shows higher cell turnover rates in neoplastic cells and different characteristics from most solid cancers, and therefore, may show TLS more frequently than expected or reported up to present time. A previous study demonstrated that TLS associated with therapy involves higher levels of phosphorus due to cell destruction and STLS involves lower levels of phosphorus due to its reutilization in the synthesis of new tumor cells [8]. However, our patient showed hyperphosphatemia without a prior history of therapy despite STLS, which did not correspond with the previous concept of phosphate levels as a discriminating tool between STLS and TLS associated with therapy.

A recent study [4] demonstrated that the striking characteristics of STLS in SCLC include a high incidence of hepatic metastasis, which is found in most cases of STLS in SCLC, that predispose the patient to develop STLS because of a high tumor burden, high purine levels, or decreased uric acid clearance. However, they reported a case of STLS in SCLC in a patient presenting with hyperphosphatemia and

hyperuricemia, but without hepatic metastasis [4]; our patient also showed identical results. Therefore, it cannot be precisely stated that the typical STLS in SCLC shows hepatic metastasis at diagnosis, and further studies are required to confirm the previous concept.

In conclusion, we report here a case of STLS associated with BM metastatic SCLC without hepatic metastasis at diagnosis, and to our best knowledge, this is the first case report of STLS associated with BM metastatic SCLC in Korea.

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Characteristics and survival of patients with atypical chronic myeloid leukemia

TO THE EDITOR: BCR/ABL-negative or atypical chronic myeloid leukemia (CML; aCML) is a rare hematologic malignancy with an estimated incidence of 1-2% among all BCR/ABL-positive CML cases [1, 2]. Due to its rarity, no prospective study has been conducted to optimize a treatment strategy for BCR/ABL-negative CML; consequently, BCR/ABL-negative CML is managed with palliative therapy. A population-based study on aCML outcome is rare. Thus, aCML characteristics and outcomes were analyzed using the National Health Information Database (NHID) [3, 4].

Patients diagnosed with aCML (International Classification of Diseases, Tenth Revision, C922) between 2004 and 2015 were included. Patients 1) aged <20 years, 2) who received chemotherapy before the aCML diagnosis, and 3) for whom C922 was recorded just once during the follow-up period were excluded. Data on age, sex, insurance premiums imposed on patients proportionate to their income, location of the medical institution, transfusion history, prescription

Table 1. Characteristics of atypical chronic myeloid leukemia patients.

	N=54
Median age at diagnosis, yr (range)	73 (26-90)
≤ 65, N (%)	15 (27.8)
> 65, N (%)	39 (72.2)
Sex, male, N (%)	35 (64.8)
Income	
High, N (%)	35 (64.8)
Low, N (%)	19 (35.2)
Location of the institution	
Capital (Seoul), N (%)	20 (37.0)
Other, N (%)	34 (63.0)
Transfusion, N (%)	49 (90.7)
RBC transfusion only, N (%)	17 (31.5)
Platelet transfusion only, N (%)	0 (0.0)
RBC and platelet transfusions, N (%)	32 (59.3)
Median number of transfused packed RBC per mo, (range)	2.6 (0.2-8.5)
Medication	
Hydroxyurea, N (%)	50 (92.6)
Azacitidine, N (%)	0 (0.0)
Decitabine, N (%)	7 (13.0)
Cytarabine, N (%)	8 (14.8)
Hematopoietic stem cell transplantation, N (%)	0
Progression to acute myeloid leukemia, N (%)	5 (9.3)
Median time to acute myeloid leukemia progression, mo (range)	5 (1-30)
Death, N (%)	47 (87.0)

Abbreviation: RBC, red blood cell.