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Palliative Radiotherapy Induced Severe Tumor Lysis Syndrome in a Patient With Multiple Myeloma With Skin Involvement: A Case Report and Review of Literature

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Abstract. *Background/Aim: Radiotherapy (RT) has been rarely reported as a cause of tumor lysis syndrome (TLS). Therefore, the patient characteristics and details of RT-induced TLS remain unclear, which may delay diagnosis. Herein, we report a case of palliative RT-induced severe TLS in a patient with multiple myeloma (MM) with skin involvement along with literature review. Case Report: A 75-year-old female with MM was referred to our department in February 2021 because of swelling and pruritus of the bulky tumor on her right breast and severe left leg pain. She had received chemotherapies and autologous peripheral blood stem cell transplantations since October 2012. We administered palliative RT (a single 8 Gy fraction) to the right breast, left tibia, and femur. On day 7 after RT, a shrinkage effect was observed on the right breast lesion, and left leg pain was relieved. Her laboratory results showed hyperuricemia, hyperphosphatemia, and hypercreatininemia. Initially, we considered acute renal failure (ARF) due to MM progression and planned for a follow-up after 1 week. On day 14 after RT completion, she experienced vomiting and anorexia. Her laboratory results became worse. She was admitted with the diagnosis of TLS and received intravenous fluid hydration and allopurinol. Unfortunately, the evolution was marked by severe clinical deterioration with anuria and coma, leading to death on day 35 after RT. Conclusion: It is important to determine whether ARF is due to MM progression or TLS. The occurrence of TLS should be considered in the case of a rapidly shrinking bulky tumor while receiving palliative RT.*

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Tumor lysis syndrome (TLS) is an important oncological emergency that requires immediate diagnosis and interventional treatment. TLS is generally triggered by chemotherapy for rapidly growing malignancy, especially acute leukemia, and high-grade lymphoma. Currently, there are limited reports regarding radiotherapy (RT)-induced TLS (1). Therefore, the patient characteristics and details of RT-induced TLS remain unclear, which may delay diagnosis. Herein, we report a case of palliative RT-induced severe TLS in a patient with multiple myeloma (MM) with skin involvement along with literature review.

Case Report

The case was a 75-year-old female with a medical history of asthma. In October 2012, she was diagnosed with stage I MM [Revised International Staging System (2)] and received six cycles of bortezomib and dexamethasone chemotherapy, to which she had a complete response. Thereafter, she received autologous peripheral blood stem cell transplantation (auto-PBSCT) and bortezomib as maintenance chemotherapy in July 2013. In July 2015, her MM relapsed, and she received nine cycles of lenalidomide and dexamethasone chemotherapy, to which she had a complete response. Next, she received a second auto-PBSCT and bortezomib as maintenance chemotherapy in September 2016. However, her MM relapsed again. She received four cycles of pomalidomide and dexamethasone chemotherapy in December 2017; nine cycles of daratumumab, lenalidomide, and dexamethasone chemotherapy in April 2018; 13 cycles of carfilzomib, pomalidomide, and dexamethasone

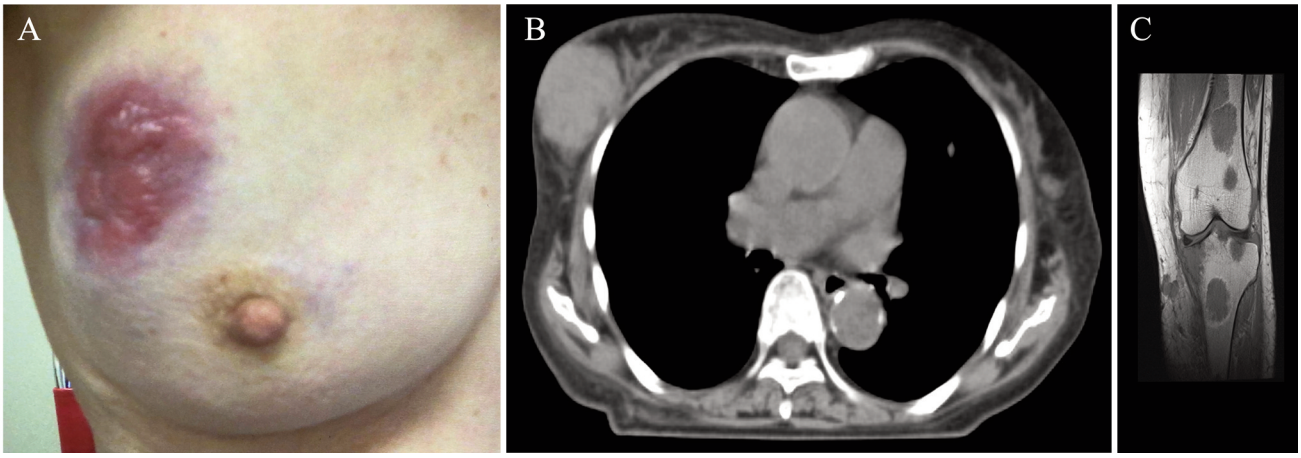

Figure 1. *Pretreatment appearance (A) and computed tomography (B) images of the right breast. (C) Pretreatment magnetic resonance imaging of the left leg.*

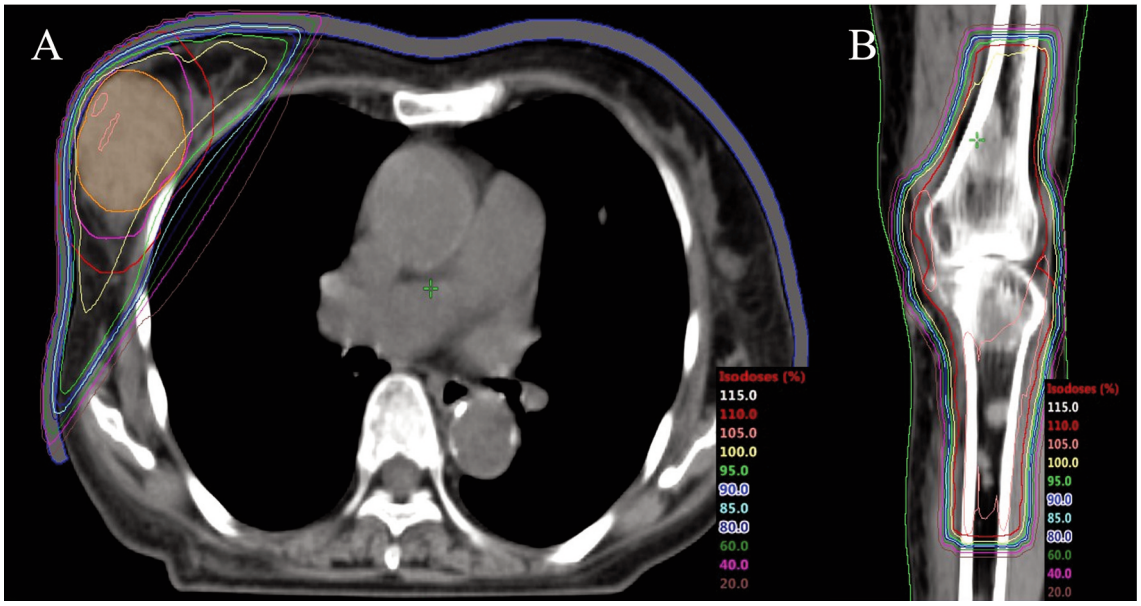

Figure 2. *Dose distribution of the right breast (A) and left leg (B).*

chemotherapy in January 2019; 13 cycles of elotuzumab, pomalidomide, and dexamethasone chemotherapy in March 2020; two cycles of weekly carfilzomib and dexamethasone chemotherapy in December 2020; and one cycle of isatuximab, pomalidomide, and dexamethasone chemotherapy in January 2021. She presented with multiple skin and bone lesions. At this point, she decided to receive the best supportive care. She was referred to our department in February 2021 because of swelling and pruritus of the bulky tumor on her right breast and severe left leg pain (Figure 1). Magnetic resonance imaging revealed osteolytic bone lesions. Her Eastern Cooperative Oncology Group performance status was 3 because of severe left leg pain. Before RT, her laboratory results were as follows: uric acid 4.6 mg/dl, potassium 3.4 mEq/l, phosphorus 4 mg/dl, calcium 8.8 mg/dl, sodium 145 mEq/l, creatinine 0.64 mg/dl, and lactate dehydrogenase (LDH) 296 IU/l. We administered palliative RT (a single 8 Gy fraction) to the bulky tumor on her right breast, left tibia, and femur (Figure 2). The size of the bulky tumor was 8×4×4 cm. The gross tumor volume, clinical target volume, and planning target volume were 61, 119, and

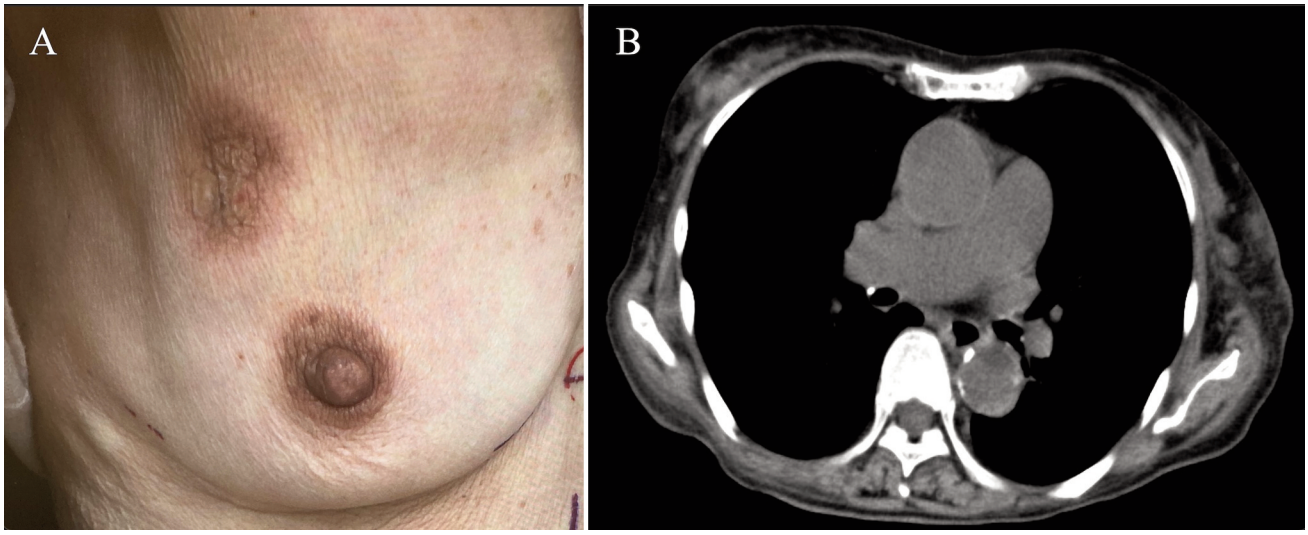

Figure 3. *Posttreatment appearance (A) and computed tomography (B) images of the right breast.*

Table I. *Laboratory results of the patient.*

Parameters	Before radiotherapy	Day 7	Day 14	Day 21	Day 28
Uric acid (mg/dl)	4.6	7.7	13	6.7	6.7
Potassium (mEq/l)	3.4	3.7	4.2	4.1	4.1
Phosphorus (mg/dl)	4	6	6.1	3.2	5.8
Calcium (mg/dl)	8.8	8.3	8.1	8.2	6.8
Sodium (mEq/l)	145	145	144	143	136
Creatinine (mg/dl)	0.64	1.98	4.42	5.84	6.32
Lactate dehydrogenase (IU/l)	296	255	201	240	441

214 cc for the right breast and 18, 280, and 482 cc for the left leg, respectively. On day 7 after RT, a shrinkage effect was observed on the right breast lesion, and left leg pain was relieved. Her laboratory results were as follows: uric acid 7.7 mg/dl, potassium 3.7 mEq/l, phosphorus 6 mg/dl, calcium 8.3 mg/dL, sodium 145 mEq/l, creatinine 1.98 mg/dl, and LDH 255 IU/l. Initially, we considered acute renal failure (ARF) due to MM progression and planned for a follow-up after 1 week. On day 14 after RT, her right breast lesion was almost gone (Figure 3). However, she experienced vomiting and anorexia. Her laboratory results became worse (Table I). She was admitted with the diagnosis of TLS. She received intravenous fluid hydration and allopurinol according to the TLS treatment guidelines. Blood and urine cultures were drawn, and cefepime was initiated since aspiration pneumonia was suspected. Serial laboratory examinations showed increased creatinine levels and decreased uric acid levels (Table I). Unfortunately, the evolution was marked by severe clinical deterioration with anuria and coma, leading to death on day 35 after RT.

Discussion

We experienced a case of palliative RT-induced severe TLS in a patient with MM with skin involvement. The clinical course of this case is notable in that it was difficult to diagnose whether the renal failure was due to MM or TLS and that TLS occurred in association with the rapid shrinkage of the bulky tumor.

We could not diagnose her as having TLS at the first follow-up period because of the following reasons: First, we considered that ARF was due to MM progression because of her long clinical course. Renal failure is a common feature of MM. Studies have shown that renal failure is associated with poor survival (3). However, hypercalcemia is the common cause of renal failure in MM (3, 4). On the other hand, TLS is characterized by biochemical variables such as hyperuricemia, hyperphosphatemia, hyperpotassemia, and hypocalcemia (5). In our case, her laboratory results showed hyperuricemia, hyperphosphatemia, hypercreatininemia, and

Table II. *Radiotherapy induced tumor lysis syndrome of previous reports*.

Author (Ref)	Year	Sex	Age	Primary malignancy	Intent of RT	RT site	Tumor size	Pre-scribed dose (Gy)	Fraction	UA before RT (mg/dl)	Cr before RT (mg/dl)	LDH before RT (IU/l)	Days from end of RT to blood test (days)	UA (mg/dl)	Po (mEq/l)	Ph (mg/dl)	Ca (mg/dl)	So (mEq/l)	Cr (mg/dl)	LDH (IU/l)	Treatments	Survival time from end of RT (days)
Tomlinson (7)	1984	M	34	Medullo-blastoma	Palliative	Pelvis	NS	3	1	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	Allopurinol, alkaline diuresis, hydration	Alive
Malik (8)	1992	M	38	CLL	Palliative	Spleen	NS	NS	5	NS	NS	NS	3	50	8,3	31,5	5,9	133	5	NS	Allopurinol, aludrox, hydration	Alive
Schifter (9)	1999	M	72	NHL	Palliative	Spleen	NS	5	10	11,5	1,8	648	2	33,7	6,1	13,7	6,8	NS	3,4	2231	Dialysis	NS
Rostom (10)	2000	F	73	Breast cancer	Palliative	Hemi-body	NS	8,5	1	7,7	0,77	NS	4	21,9	5,7	NS	8,1	135	2,04	NS	Allopurinol, calcium carbonate, hydration	8 days
Yamazaki (11)	2004	M	74	NHL	Palliative	Media-stinum	Bulky	6	3	8,3	2,7	2900	4	6,8	5	NS	7,9	NS	7,7	1566	(Prophylactic) allopurinol, dialysis	7 days
Chen (12)	2005	M	74	CLL	Palliative	Spleen	NS	0,5	1	7,4	2,7	1.604	3	9,5	7,6	13,2	NS	NS	3,1	911	Dialysis	Alive
Noh (13)	2008	M	52	NSCLC	Palliative	Media-stinum	10 cm	30	10	NS	NS	NS	2*	8,9	6,1	6,2	8,5	NS	1,4	3331	Sodium bicarbonate, furosemide, hydration, dialysis	1 day
Jain (14)	2010	M	66	Myelo-fibrosis	Palliative	Spleen	34.5× 22 cm	1	1	NS	NS	NS	7	NS	6	9,3	7,4	NS	2,62	NS	Allopurinol, hydration	Alive
Kaplan (15)	2012	M	60	Prostate cancer	Palliative	Shoulder	NS	30	10	4,1	1,5	1173	6*	15,6	5,9	6	6,9	NS	4,5	6695	Sodium bicarbonate	11 days
Dar (16)	2014	M	65	Melanoma	Palliative	Pelvis, shoulder	NS	NS	5	NS	NS	NS	7	18,5	5,3	7,9	10,4	137	3,7	NS	Allopurinol, rabruricase, hydration	28 days

Table II. *Continued*

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Author (Ref)	Year	Sex	Age	Primary malignancy	Intent of RT	RT site	Tumor size	Pre-scribed dose (Gy)	Fraction	UA before RT (mg/dl)	Cr before RT (mg/dl)	LDH before RT (IU/l)	Days from end of RT to blood test (days)	UA (mg/dl)	Po (mEq/l)	Ph (mg/dl)	Ca (mg/dl)	So (mEq/l)	Cr (mg/dl)	LDH (IU/l)	Treatments	Survival time from end of RT (days)
Alkan (17)	2015	M	69	CLL	Palliative	Spine, shoulder	NS	30	10	6,7	1,6	320	6	14,6	6,1	7,2	8,4	132	7,1	732	Rabruricase, hydration, dialysis	Alive
Stuart (18)	2017	M	Middle age	Broncho-genic adeno-carcinoma	Palliative	NS	NS	NS	NS	NS	NS	NS	3	15,8	7,1	6,2	6,4	NS	5,7	NS	Allopurinol, rabruricase, hydration	Alive
Yavo-rkovsky (19)	2020	F	79	MM	Palliative	Rib	NS	NS	NS	7,6	1,2	NS	1	12,6	NS	NS	6,9	NS	7,39	NS	NS	21 days
Yavo-rkovsky (19)	2020	M	77	MM	Palliative	Cervical lymph nodes	NS	NS	NS	8,8	1,26	NS	7	11,8	NS	NS	6,8	NS	8,22	NS	NS	35 days
Cailleteau (20)	2022	F	53	MM	Palliative	Forearm	NS	20	4	2,2	0,79	NS	4*	5,1	5,1	6,8	8	NS	1,45	542	Hydration	NS
Schiff (21)	2022	F	85	Endometrial cancer	Palliative	Pelvic mass	13×9× 9 cm	20-67 (SIB)	5	NS	1,76	NS	13	17,6	6,4	3,8	9	NS	2,82	370	Calcium gluconate, insulin-dextrose, albuterol, sodium zirconium cyclosilicate, rabruricase	NS (dead)
Our report	2022	F	74	MM	Palliative	Breast, tibia, and femur	8×4× 4 cm	8	1	4,6	0,64	296	7	7,7	3,7	6	8,3	145	1,98	255	Allopurinol, hydration	35 days

Ca: Calcium; CLL: chronic lymphocytic leukemia; Cr: creatinine; F: female; LDH: lactate dehydrogenase; M: male; MM: multiple myeloma; NHL: non-Hodgkin lymphoma; NS: not stated; NSCLC: non-small cell lung cancer; Ph: phosphorus; Po: potassium; RT: radiotherapy; SIB: simultaneous integrated boost; So, sodium; US: uric acid. *From start of RT.

normal calcium revels. The normal calcium levels were probably because the hypercalcemia from terminal MM masked the hypocalcemia from TLS. Laboratory TLS is defined as the presence of at least two or more biochemical variables within 3 days before chemotherapy or 7 days after chemotherapy (6). Clinical TLS is defined as laboratory TLS complicated by clinical manifestations such as arrhythmia, renal failure, seizure, and sudden death (6). However, this definition is not perfect since RT may lead to TLS and TLS can occur spontaneously in a rapidly proliferating and bulky tumor. Collectively, we should have diagnosed the patient as having clinical TLS at the first follow-up period despite receiving RT. Second, RT and MM can rarely cause TLS. A review article reported that chemotherapy was the most frequent cause of TLS (57%), followed by spontaneity (26%), glucocorticoid (7%), RT (3%), and others (7%). Among hematologic malignancies as a cause of TLS, the most common is leukemia (48%), followed by non-Hodgkin lymphoma (39%), MM (11%), and Hodgkin lymphoma (2%) (1).

Table II shows the available reports on RT-induced TLS (7-21). Two studies reported three cases of RT-induced TLS in MM (19, 20). In another study, all 16 cases developed TLS after the initiation of RT (1). Fifteen cases received palliative RT (≤30 Gy) except one. There were many reports of relatively large irradiation fields, such as the hemi-body and spleen, and bulky tumor. Previous reviews reported that the larger the cancer mass or the higher the number of cells that will lyse with chemotherapy, the higher the risk of clinical TLS (6). TLS needs to be suspected in the case of a rapidly shrinking bulky tumor. According to the treatment guidelines for MM, a single 8 Gy fraction is preferred for bone lesions in patients with poor condition (22). Although the appropriate dose for a skin lesion remains unknown because of its rare occurrence (23), a single 8 Gy fraction was acceptable with regard to our patient's condition. Previous studies reported that elevated pretreatment levels of LDH, creatinine, and uric acid were risk factors for TLS in patients with acute myeloid leukemia and solid tumor (24-26). The available laboratory results also showed elevated pretreatment levels of LDH. Prophylactic treatments including allopurinol, hydration prior to treatment, and urine alkalization are important for patients at risk of TLS (27). In the future, new strategies such as concurrent RT with immune checkpoint inhibitor therapy need to be developed to treat patients with TLS.

In conclusion, it is important to determine whether ARF is due to MM progression or TLS. The occurrence of TLS should be considered in the case of a rapidly shrinking bulky tumor while receiving palliative RT. Prophylactic treatments including allopurinol, hydration prior to treatment, and urine alkalization are important for patients at risk of TLS.

Conflicts of Interest

The Authors declare no conflicts of interest in relation to this study.

Authors' Contributions

Terufumi Kawamoto prepared the manuscript and conducted the literature search, reviewed and edited the manuscript. TK, YM, MO, YK, and NS reviewed the manuscript. All Authors have read and approved the final manuscript.

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