Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.0893-22
Intern Med 62: 3075-3084, 2023
http://internmed.jp

【 CASE REPORT 】

Malignancy-related Hypercalcemia Caused by Metameric Cutaneous Metastasis of Parathyroid Hormone-related Protein-producing Bladder Carcinoma with Squamous Cell Differentiation: An Autopsy Case of Cobb Syndrome

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Abstract:

A 74-year-old woman was admitted with hypercalcemia and prolonged disturbance of consciousness. The left buttock to the anterior aspect of the left thigh was swollen and erythematous, with a collection of 1.0-cm large, firm, elastic nodules distributed in a zosteriform pattern in the L1-L4 region. Based on autopsy findings, a very rare case of Cobb syndrome was diagnosed due to a spinal vascular malformation at the Th12-L4 level and L5 vertebral hemangioma. Cobb syndrome-associated cutaneous metastasis extending along the same metamere was complicated by immunohistochemically proven parathyroid hormone-related protein-producing advanced bladder carcinoma in this case.

Key words: Cobb syndrome, bladder squamous carcinoma, cutaneous metastasis, parathyroid hormone-related protein-C producing tumor, malignancy-related hypercalcemia

(Intern Med 62: 3075-3084, 2023)
(DOI: 10.2169/internalmedicine.0893-22)

Introduction

Cobb syndrome, a rare condition first described by Stanley Cobb in 1915 (1), is a non-hereditary neurocutaneous syndrome characterized by spinal vascular abnormalities in association with cutaneous vascular lesions at the same metamere (2). It was recently characterized as "spinal arteriovenous metameric syndrome (SAMS)" because it is associated with arteriovenous malformations (AVMs) or arteriovenous fistulas of the spinal cord and vascular malformations of the skin originating from the same metameric level (3-5). It is classified into the subgroup of vascular malformations associated with other abnormalities according to the International Society for the Study of Vascular Abnormalities (ISSVA) classification for vascular abnormalities (6, 7).

Bladder cancer is a malignant tumor arising from the uroepithelial mucosa of the bladder, with >90% of cases being uroepithelial carcinomas, 8% being squamous cell carcinomas, and <2% being adenocarcinomas (8). The incidence of bladder carcinoma in men is about four times that in women. Ninety-two percent of bladder carcinomas occur after 60 years old. Deaths from bladder carcinoma account for 2.2% of all malignant neoplasm-related deaths. However, cutaneous metastases from urologic tumors are uncommon. The incidence of cutaneous metastases from the bladder was only 0.84% (9).

Malignancy-related hypercalcemia occurs in approximately 20% of all cancer patients during their clinical course (10), although bladder carcinoma patients rarely show this finding. Excessive secretion of parathyroid hormone-related protein-C (PTHrP) by malignant tumors is responsible for 80% of the cases of malignancy-related hy-

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Received: August 24, 2022; Accepted: January 23, 2023; Advance Publication by J-STAGE: March 1, 2023
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percalcemia (11), which is usually seen in cases of solid tumors. The common solid tumors associated with this finding include squamous cell carcinomas of the head, neck, and lungs; breast cancer; ovarian cancers; renal carcinoma; and rarely, bladder carcinoma (10).

We herein report an extremely rare autopsy case of Cobb syndrome showing malignancy-related hypercalcemia caused by asymmetric metameric (zosteriform) cutaneous metastasis of PTHrP-producing bladder urothelial carcinoma with squamous cell differentiation.

Case Report

A 74-year-old woman was transferred to our hospital with impaired consciousness. The patient had been experiencing cellulitis of the left lumbar region to the left thigh for the past four years, which recurred every few months. Each time, the patient was prescribed antibacterial medication of cefcapene pivoxil 300 mg/day by her local dermatologist, and the cellulitis was ameliorated. One month before admission, two to three elastic but hard nodular cutaneous erythematous papules appeared on her left thigh. Subsequently, the papules gradually expanded in size and became more prominent. Ten days prior to admission, she visited a dermatologist but was told to wait and see how her condition progressed. Eight days prior to admission, she had visions of "insects walking around, red walls," etc. She lost her appetite and became somnolent. She was oliguric, and pyuria was noted from the urethral balloon catheter. Three days prior to admission, she was urgently admitted to the previous hospital due to progressive loss of consciousness and an inability to move. She was transferred to our department for a further examination and treatment because of hypercalcemia (17.5 mg/dL), leukocytosis (26,000/μL), and a high C-reactive protein level (11.0 mg/dL).

Her medical history included that she had experienced unspecified acute onset paraplegia after giving birth to a baby girl by Caesarean section at 25 years old and later been confined to a wheelchair. At 40, 49, and 50 years old, she had undergone open knee-to-hip drainage and left hip arthrodesis for left pyogenic hip arthritis and left knee arthritis, hysterectomy for uterine myoma and ovarian tumor, and urethral balloon replacement for urinary retention, respectively. At 72 years old, she underwent aortic Y-shaped Hemashield artery replacement and greater omentum patch closure at the same site for ruptured lumbar aneurysm, after which antihypertensive treatment was started. In the same year, she had undergone open drainage and jejunostomy for perforative peritonitis due to small bowel perforation. She had then undergone central venous port implantation in the right upper extremity and colostomy of the jejunostomy. At the present admission, a pale reddish skin tone change from the left inguinal area to the anterior aspect of the thigh was observed (arrows of Supplementary material).

The medications were bisoprolol, 2.5 mg/day; rabeprazole, 10 mg/day; limaprost, 15 μg/day; mecobalamin, 1,500 μg/day; and magnesium oxide, 750 mg/day. Her family history was unremarkable for cardiovascular diseases and genetic diseases. She did not smoke or drink alcohol and was wheelchair-bound and required level 2 nursing care.

A physical examination on admission showed swelling of the left buttock that kept the patient in the right-side supine position; she frowned with pain when she moved her body. Her level of consciousness was Japan coma scale (JCS) II-10 and Glasgow coma scale (GCS) E3V4M5. Her vital signs were as follows: temperature, 35.8°C; pulse, 72/min; blood pressure, 95/45 mmHg; respiratory rate, 12 breaths/min; and SpO_2 99% on ambient air. She showed conjunctival anemia, no icterus of the ocular conjunctiva, and no cervical lymphadenopathy. A surgical scar and an abdominal wall scar hernia was observed in the midline of the abdomen, with no abdominal tenderness. Bilateral costovertebral angle tenderness was noted. The left inguinal area and left buttock to the anterior aspect of the left thigh were erythematous and swollen. A 1.0-cm nodule of elastic hardness with relatively clear and erythematous borders was clustered in the region of the left first to fourth lumbar vertebrae levels (Fig. 1). A urethral balloon catheter was placed in the bladder, and white pus discharge was noted at catheter removal. The external urethral orifice was hard. Incomplete paralysis of both lower extremities was noted.

A urinalysis showed the following findings: specific gravity, 1.013; pH 8.0; protein, 3+; sugar, -; acetone body, -; bilirubin, -; nitrite, -; occult blood, 3+; and bacteria, 2+. Laboratory examinations revealed the following: white blood cells (WBCs), 21,930/μL [reference range (RR), 3,900-9,800/μL]; neutrophils, 90% (RR, 40-74%); red blood cells, 299×10^4/μL (RR, $427\text{-}570\times10^4$/μL); hemoglobin, 9.4 g/dL (RR, 12-17.6 g/dL); mean corpuscular volume, 94.6 fl (RR, 83-101 fl); platelet cell count, 233,000/μL (RR, 130,000-369,000/μL); total protein, 6.3 g/dL (RR, 6.6-8.1 g/dL); albumin, 2.6 g/dL (RR, 4.1-5.1 g/dL); sodium, 133 mmoL/L (RR, 138-145 mmoL/L); potassium, 3.1 mmoL/L (RR, 3.6-4.8 mmoL/L); chloride, 99 mmoL/L(RR, 100-110 mmoL/L); calcium, 16.3 mg/dL (RR, 8.4-10.1 mg/dL); phosphorus, 4.2 mg/dL (RR, 2.7-4.6 mg/dL); blood urea nitrogen, 46 mg/dL (RR, 8-20 mg/dL); creatinine, 2.38 mg/dL (RR, 0.65-1.07 mg/dL); uric acid, 12.2 mg/dL (RR, 3.7-7.8 mg/dL); C-reactive protein, 10.2 mg/dL (RR, 0-0.14 mg/dL); D-dimer, 17.1 μg/mL (RR, 0.0-1.0 μg/mL); erythrocyte sedimentation rate, 18 mm/h (RR, 0-10 mm/h); procalcitonin, 0.73 ng/mL (RR, <10.5 mg/mL); squamous cell carcinoma-associated antigen, 182.9 ng/mL (RR, <1.5 ng/mL); and granulocyte colony-stimulating factor (G-CSF), 36.7 pg/mL (RR, 5.78-27.5 pg/mL). The results of other laboratory tests were normal. Chest radiography showed a central venous catheter in the right internal jugular vein and its port, a chest thoracic ratio of 50%, and decreased permeability in the right lower lung field.

Abdominopelvic computed tomography (CT) on admission revealed spinal scoliosis, a generalized thickening of the bladder wall, and bladder balloon catheterization

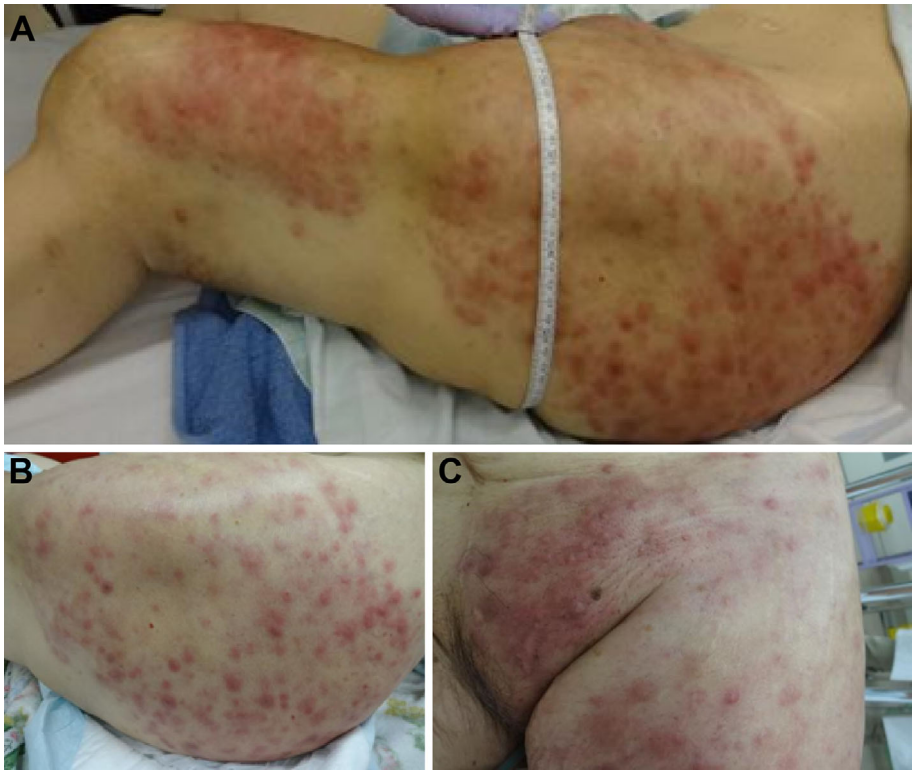

Figure 1. **(A) The left buttock extending to the left lateral aspect of the left thigh was erythematous and swollen. The border of the cutaneous lesion was clear, resembling a zosteriform pattern with 1.0-cm erythematous elastic hard nodules clustered around the metamere from the left first to fourth lumbar vertebrae levels. (B) Skin findings on the lateral aspect of the left buttock. (C) The cutaneous lesion appeared on the left side of the pubic area.**

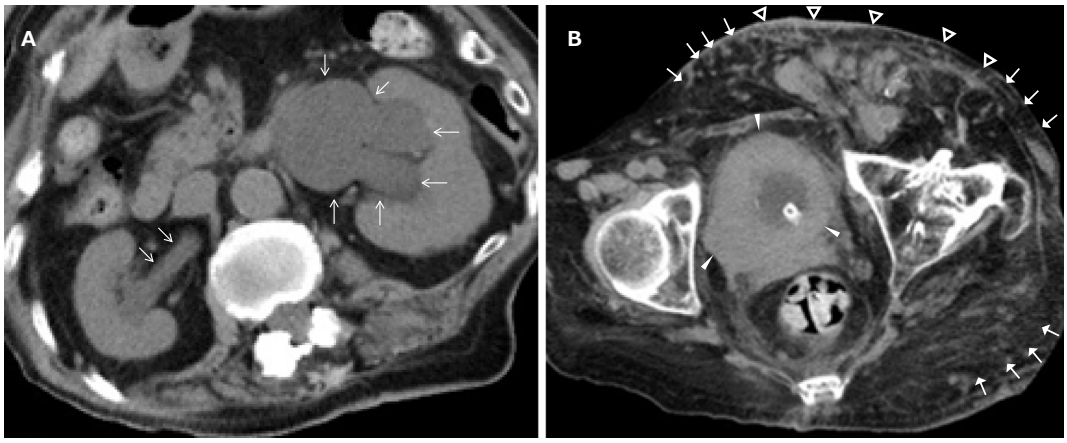

Figure 2. **Simple computed tomography of the abdomen and pelvis on admission. (A) The renal pelvises were dilated (arrows), predominantly on the left side. (B) Generalized thickening of the bladder wall (closed arrowheads) and bladder balloon catheterization were observed. Subcutaneous structures of irregular size and form (open arrowheads) and marked subcutaneous edematous changes (closed arrows) were seen in the left pelvis, inguinal area, buttocks, and thigh.**

(Fig. 2). The renal pelvises were markedly dilated, predominantly on the left side, and both ureters were dilated to the vesicoureteral junction. Skin lesions from the left buttock to the anterior aspect of the left thigh, subcutaneous structures of irregular size and irregular form (open arrowheads in Fig. 2B), and marked subcutaneous edematous thickening (closed arrows in Fig. 2B) were seen. Enhanced whole-body CT (Fig. 3) showed postoperative changes in Th12-L3 vertebrae and dilated venous vascular structures on the paravertebral left side of the fourth lumbar vertebra, as well as erratic calcified lesions in the dural sac of the spinal canal at the level of the second to the fourth lumbar vertebra, indicating

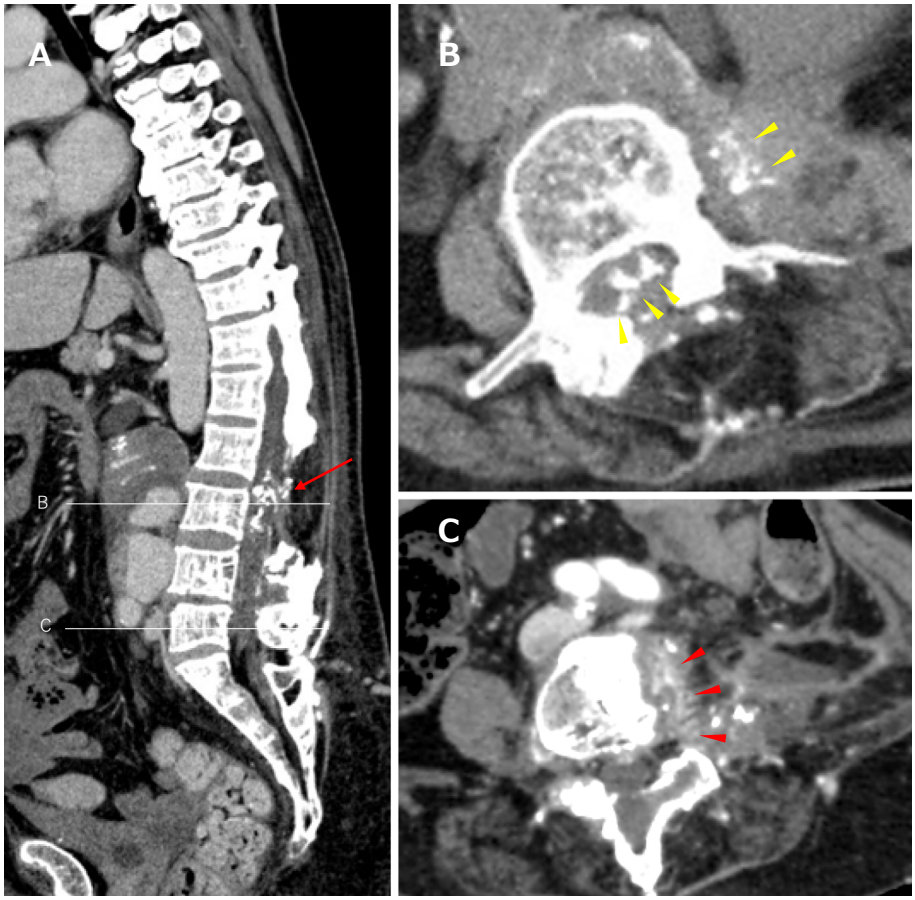

Figure 3. **Contrast-enhanced whole-body computed tomography. (A) The sagittal image showed the postoperative changes in the Th12-L3 spinal canal (closed red arrows). (B) The axial image at the third lumbar body level showed erratic calcified lesions in the spinal canal and left paravertebral area (yellow arrowheads). (C) The axial image at the fifth lumbar body level showed bone destruction on the left side of the vertebral body with an abnormal contrast effect indicating vertebral hemangioma (red arrowheads).**

spinal vascular malformations. In addition, the fifth lumbar paravertebral body level showed bony destruction images with a contrast effect, which were considered to indicate vertebral hemangiomas.

We reviewed the contrast whole-body CT findings obtained before the lumbar aneurysm rupture at 70 years old (Fig. 4) at a previous hospital. The findings showed a left lumbar aneurysm with a maximum diameter of 49 mm from the level of the second through the third lumbar vertebrae. The aneurysm was compressing the abdominal aorta to the right. The median sacral artery was developed and dilated. Malformation of blood vessels had already developed under the skin of the left groin to the anterior aspect of the left thigh.

The diagnosis of Cobb syndrome was made based on the presence of spinal vascular malformation at the L2-L4 level, L5 vertebral hemangioma, and cutaneous vascular lesions consistent with the same metamere.

The clinical course is summarized in Fig. 5. On hospital day (HD) 1, the patient was diagnosed with impaired consciousness due to hypercalcemia (corrected Ca, 17.7 mg/dL) and was started on saline infusion, 2 L; furosemide, 20 mg daily; and calcitonin, 40 units twice daily. The patient was started on a regimen to treat a tentative diagnosis of urinary tract infection with 2.25 g of piperacillin/tazobactam 3 times a day and underwent both a cytological examination of the urine and a biopsy of the cutaneous nodule in the left thigh. On HD 2, her temperature rose to 38.0°C, and her inflammatory findings did not improve; therefore, on HD 3, the antimicrobial agent was changed to meropenem (MEPM) at 0.5 g twice daily and daptomycin (DAP) at 350 mg/48 h.

On HD 3, the results of the biopsy indicated an invasion of metastatic urothelial carcinoma with squamous differentiation in the dermis and subcutaneous fatty tissue. Capillaries and lymphatic vessels in the superficial dermis were dilated. The dermis at the metastasis was markedly degenerated and infiltrated by inflammatory cells, such as eosinophils. The epidermis was not significantly affected. A urine cytological examination revealed squamous cell carcinoma with squamous differentiation (Fig. 6). On HD 4, zoledronic acid at 4 mg/day was administered once for hypercalcemia. On HD 7, the PTHrP level (RR, <1.1 pmol/L) was 29.3 pmol/L, whereas the intact-parathyroid hormone level (RR, 10-65 pg/mL) was 11.0 pg/mL, which indicated malignancy-

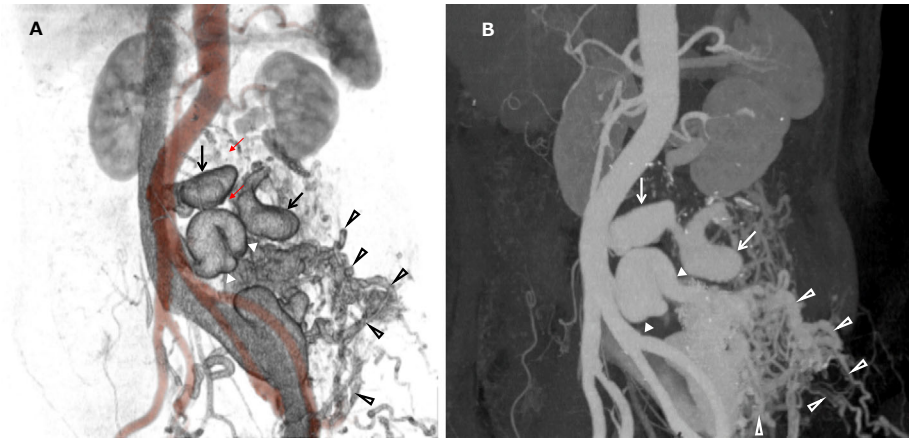

Figure 4. **(A and B) Contrast-enhanced whole-body three-dimensional computed tomography images obtained at 70 years old at a previous hospital. The arrows indicated a lumbar aneurysm before impending rupture with a maximum diameter of 49 mm at the level of the second through the third lumbar vertebrae. The aneurysm was compressing the abdominal aorta to the right. The closed arrowheads indicate the developing dilatation of the median sacral artery. The open arrowheads indicate subcutaneous malformations of angiogenesis spread in the left sides of the lumbar, buttock, and thigh.**

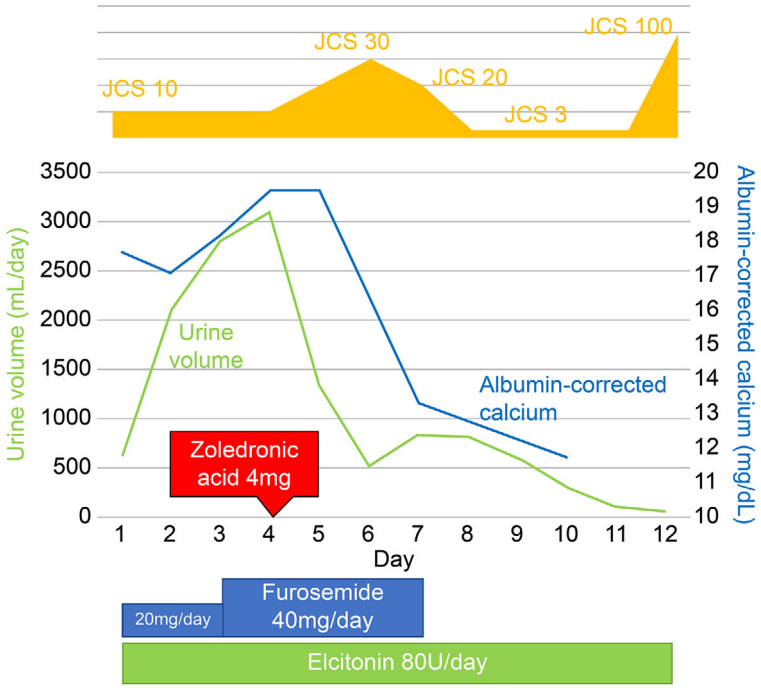

Figure 5. **The clinical course from admission to discharge including the consciousness level on the Japan coma scale (JCS), albumin-corrected calcium level (mg/dL), urinary volume (mL/day), and treatment. The level of consciousness transiently improved with the reduction in the calcium level.**

related hypercalcemia due to PTHrP-producing squamous cell carcinoma of the bladder. In addition, blood culture tests showed positive results for two sets of Bacillus species, which led to the diagnosis of sepsis. *Enterococcus faecium* was detected in urine culture; thus, the antimicrobial agent was changed from DAP to vancomycin (VCM) at 1 g once/48 h on HD 7. The level of consciousness improved to JCS I-3 around HD 7. However, renal failure worsened, and the patient became oliguric on HD 10 and died on HD 12.

An autopsy was performed with the written consent of the patient's family.

Autopsy findings

The bladder wall had thickened to 20 mm circumferentially due to tumor invasion and tumor growth. Necrosis of the bladder lumen was observed. The bladder tumor had consecutively metastasized to the small pelvic peritoneum, retroperitoneum in front of the lumbar spine, and skin from

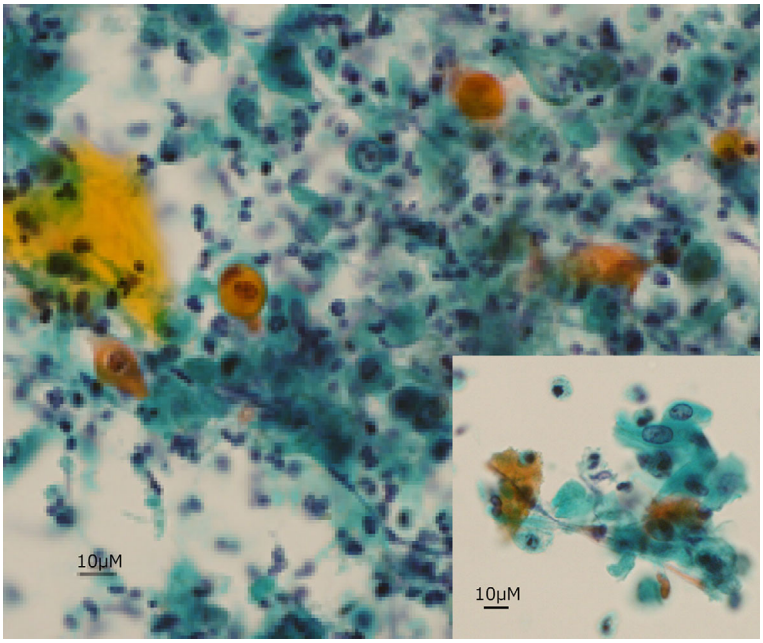

Figure 6. **A urine cytological examination (Papanicolaou stain) revealed squamous cell carcinoma with squamous differentiation.**

the left perineum to the left thigh to the buttocks. It was difficult to determine the boundary between blood-borne metastasis by lesions of Cobb syndrome and direct cutaneous metastasis from bladder cancer. However, the abnormal subcutaneous blood vessels were irregularly developed. Based on this finding, the cutaneous metastatic lesions were considered to be haematologus. The distant metastases included tumor emboli in the middle lobe of the right lung and small metastatic lesions within the cardiac left ventricular wall. Microhistopathologically, the tumor was a well-differentiated squamous cell carcinoma with well-defined keratinized foci. The skin lesions were consistent with cutaneous metastasis of primary urothelial well-differentiated squamous cell carcinoma.

Malformation of clustered blood vessels with variable wall thickening and recanalization and partial calcification was found in the lumbar spinal cord; however, the normal spinal cord could not be identified. Microscopic images showed fibrosis with hyalinization and calcification around the nerve bundles of the lumbar spinal cord. These fibrotic lesions included elastic fibers detected by Elastica van Gieson (EVG) staining, smooth muscle deformities detected by alpha-smooth muscle actin (αSMA) immunostaining, organizing dilated vascular structures with an irregular vascular wall, and sections of vascular recanalization. Most of the vessels had become remarkably organized, making it difficult to determine their original structure; however, clusters of dilated vessels without proliferation of endothelial cells were suspected to be arteriovenous or venous malformations. The autopsy findings supported our clinical reasoning for a diagnosis of Cobb syndrome.

An immunohistochemical examination

An immunohistochemical examination was performed using bladder cancer tissue and skin metastasis tissue. Immunohistochemical staining with a rabbit anti-PTHLH antibody [SIGMA-ALDORICH (Merck) HPA035982] as the PTHrP antibody showed predominantly positive results for the tumor cells in bladder tumors and skin metastases in comparison with the negative control (Fig. 7). Thus, we believe that the bladder tumor and skin metastases were PTHrP-producing tumors.

Discussion

Cobb syndrome, also known as SAMS and cutaneous meningospinal angiomatosis, is extremely rare. Furthermore, no previous report has described Cobb syndrome patients with malignancy-related hypercalcemia caused by metameric cutaneous metastasis of PTHrP-producing bladder carcinoma with squamous cell differentiation. This report highlighted three critical clinical issues. First, it aimed to clarify whether or not the clinical diagnosis of Cobb syndrome was reasonable. Second, it aimed to clarify whether or not the characteristic metameric cutaneous metastasis pattern of bladder urothelial carcinoma in this patient was associated with Cobb syndrome. Finally, it aimed to determine whether or not this patient's bladder carcinoma was producing PTHrP.

First, Cobb syndrome is considered to be a form of spinal arteriovenous metameric syndrome characterized by vascular malformations of the spinal cord, dura mater, vertebral body, paravertebral tissue, muscles, and skin that develop in the same body somite (metamere). The differences between the clinical and radiological features of Cobb syndrome and

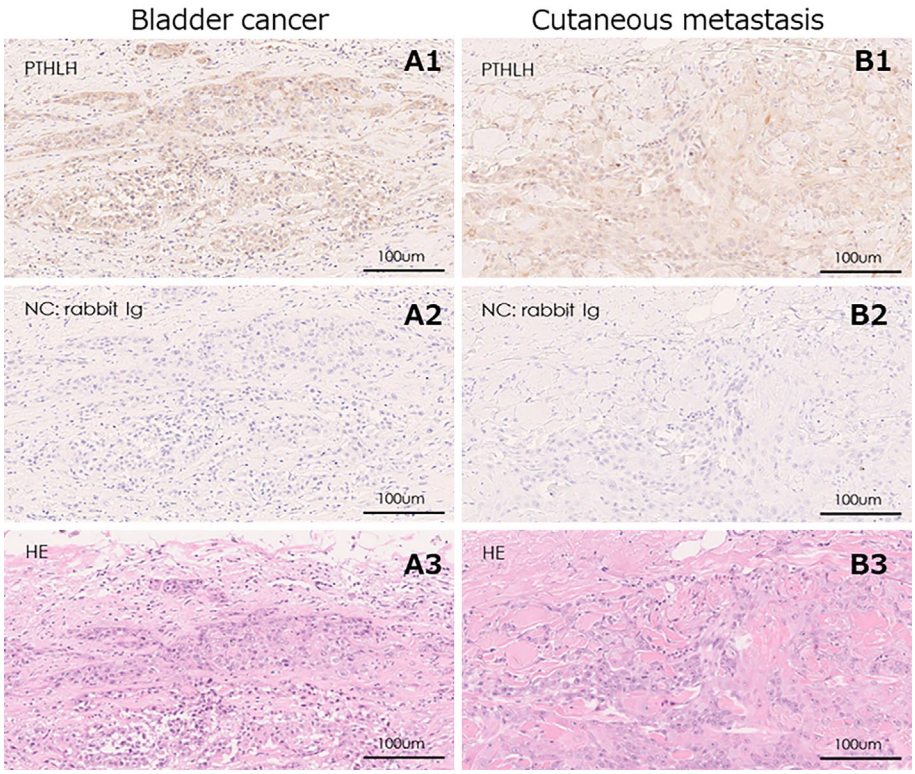

Figure 7. **Immunohistochemical staining of the bladder cancer tissue and the skin metastasis tissue using rabbit anti-parathyroid hormone-related protein (PTHLH) antibody [SIGMA-ALDORICH (Merck) HPA035982] as the PTHrP antibody for comparison with the negative control (NC) using anti-rabbit IgG antibody (rabbit Ig). Panel A indicates the results of bladder cancer stained by PTHLH (A1), rabbit Ig (A2), and Hematoxylin and Eosin (H&E) staining (A3). Panel B indicates the results of cutaneous metastasis stained by PTHLH (B1), rabbit Ig (B2), and H&E staining (B3). These tumor cells in bladder tumors and cutaneous metastases were predominantly positive in comparison with the negative control.**

those of Klippel-Trenaunay syndrome, which is included in the differential diagnosis of Cobb syndrome, are summarized in Table 1 (12). Reviewing the medical history of the present patient, the complications were consistent with Cobb syndrome. The italicized text in Table 1 indicates the findings seen in this patient.

The present patient had a history of spinal AVM, with imaging and pathologic evidence of postoperative changes at Th12-L3, abnormal spinal vessels at L2-4, a vertebral hemangioma at L5, and cutaneous lesions of dermatome L1-4 consistent with the same segmental distribution.

The skin rash of Cobb syndrome can vary from only slight color changes to capillary malformations (port wine stain). Although the age of the onset of neurologic symptoms is usually from childhood to adolescence, we were unable to confirm whether or not our patient had had skin changes since childhood. However, she had shown a pale color change around her left inguinal area when she was admitted to our hospital two years earlier. Recently, the importance of target lesion delineation using multimodality imaging consisting of contrast-enhanced CT, magnetic resonance imaging (MRI), and digital subtraction angiography (DSA) for the diagnosis of Cobb syndrome has been reported (13).

Our patient had experienced acute-onset paraplegia of the lower extremities due to spinal cord paralysis at the time of her pregnancy. Such paraplegia has been reported to be an alarming sign of Cobb syndrome, especially when accompanied by skin lesions in the same metamere (14). We believed that the onset of symptoms occurred at this time and caused the symptoms. An onset during pregnancy is an exacerbating factor for Cobb syndrome and can be explained by the increased blood flow and venous pressure, which dilates the vessels in the hemangioma and results in spinal motor paralysis. At 40 years old, our patient underwent open drainage of the left pyogenic knee arthritis, and since then, she has shown unilateral enlargement of the left lower limb. Klippel-Trenaunay-Weber syndrome is a disorder that results from vascular malformations, such as capillary malformations, venous malformations, arterial malformations, arteriovenous fistulas, and lymphatic malformations, that cause left-right differences in the size and morphology of the upper or lower extremities. In Klippel-Trenaunay-Weber syndrome, a bacterial infection from a small wound on a limb can trigger swelling of the entire limb, resulting in pain and gait disturbances, and we wondered if this diagnosis would be applicable in the present patient.

Table 1. Comparison of Clinical and Radiologic Characteristics of Cobb Syndrome and Klippel-Trenaunay Syndrome (12).

	Cobb syndrome Cutaneomeningospinal angiomatosis (ISSVA 2014) Spinal arteriovenous metameric syndrome (SAMS)	Klippel-Trenaunay syndrome Unilateral limb enlargement Slow-flow vascular malformations (venous malformations, capillary malformations, lymphatic malformations)
Main presentation	Vascular skin nevus → *Abnormal vascular dilatation and metastatic findings in the left inguinal to thigh area under the skin to the subcutis, suspicious of vascular malformation*	Limb hypertrophy, venous varicosities → *Left unilateral limb hypertrophy present*
Radiographic findings	Spinal canal angioma at the same metamere → *Spinal cord vascular malformation of Th12-L4, with postoperative changes*	Absence of fistulas in the involved limb
Cutaneous stain	Pink to red angiomas on the back → *Pale pink tinge in left inguinal region* → *Skin metastases along the dermatome in the L1-4 region*	Large; pink to red or red to violaceous
Venous varicose	None	Always
Arteriovenous fistulas	Arteriovenous fistula of the spinal canal → *Abnormal vascular growth of L2-4, L5 vertebral hemangioma*	Absent
Overgrowth feature	None	Usually, the lower limb → *Left unilateral limb hypertrophy present*
Lymphatic malformation	Lymphangioma	Common
Bone alteration	Kyphoscoliosis → *With scoliosis*	Rarefied, osteoporosis
Brain involvement	None	Not reported
Spinal vascular disorders	Spinal AVM or cavernomas → *Surgical history of spinal AVMs*	None
Involved gene mutation	Not clear	AGGF1, PIK3CA
Age at onset	Childhood-adolescence → *Onset at age 25*	Under 5 years old

ISSVA: International Society for the Study of Vascular Anomalies, Th: thoracic vertebra, L: lumbar vertebra, AVM: arteriovenous malformation, AGGF1: angiogenic factor with G-patch and FHA domains 1, PIK3CA: phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha
The letters in italics indicate the findings seen in this patient.

Our patient underwent hystero-oophorectomy for myoma and ovarian tumors at 49 years old. The neurogenic bladder-induced urinary retention that necessitated urethral balloon placement at 50 years old was believed to have been due to the development of rectovesical disorders caused by progressive spinal cord lesions in Cobb syndrome (15). Permanent bladder catheterization may have caused mechanical and chronic irritation, which may have contributed to the development of bladder cancer (16, 17).

At 72 years old, the patient underwent Y-graft replacement and mesh filling for an infected left lumbar aortic aneurysm that had impedingly ruptured, and abnormal dilatation of the median sacral artery was noted. These findings further suggested the involvement of Cobb syndrome.

Klippel-Trenaunay-Weber syndrome is a congenital disease that often occurs before five years old, does not include spinal AVM complications in its definition, and involves slow-flow vascular malformations without causing the ruptured aneurysm seen in our present patient. This patient did not undergo any tests for genetic abnormalities related to Klippel-Trenaunay-Weber syndrome. The gradually worsening hypertrophy of her left lower limb in adulthood was attributed to lymphatic flow abnormalities and abnormal angiogenesis as Cobb syndrome and lymphedema as well as other postoperative changes, symptoms which are all acquired. Given the abovementioned medical findings in the present patient, we concluded that she did indeed have Cobb syndrome.

Second, Willis classified the routes of arrival of visceral carcinomas to the skin into hematogenous, lymphatic, direct, and disseminated metastases (18). The appearance of the cutaneous metastasis of the carcinoma along the segments in the present patient was due to Cobb syndrome, in which each segmental artery branching from the aorta nourishes the spinal cord, muscle, bone, and metameric cutaneous metastasis, resulting in abnormal blood and lymphatic flow at the same level as the abnormal angiogenesis in the spinal cord. Bladder cancer cells may have formed such a localized metameric cutaneous metastasis from the left buttock to the thigh because of hematogenous lymphatic metastasis along this abnormal vascular distribution.

Finally, this was a rare case of cutaneous metastasis of squamous cell carcinoma of the urinary bladder and a PTHrP-producing tumor. Excessive secretion of PTHrP by malignant tumors is found in 80% of patients with malignancy-associated hypercalcemia (11). PTHrP-producing

Table 2. Case Reports of Bladder Cancer with Elevated Parathyroid Hormone-related Protein and Granulocyte Colony-stimulating Factor

Age	Sex	Cancer type	Serum Ca (mg/dL)	Serum PTHrP (pmol/L)	WBC (/μL)	Serum G-CSF (pg/mL)	Prognosis	Reference number
74	F	SCC	16.3	29.3	21,930	36.7	12 days CD	Present
42	M	SCC	3.28 mmol/L =13.15	2.3	22,000	Not reported	5 months CD	(16)
47	F	TCC and partial SCC	14.0	16.9		Not reported	1 month CD	(19)
38	F	TCC	14.4	11.1	107,000	77.1	3 months CD	(20)
71	F	TCC	18.6	24.4	37,000	198	3 months CD	(21)
68	F	TCC	15	8.4	99,600	70.0	46 days CD	(22)
61	M	TCC	12	38	14,200	Not reported	5 months CD	(23)
55	M	SCC	13	4.2		Not reported		(24)
77	F	SCC	3.09 mmol/L =12.38	87 ng/L (12, 15-27)=9.2		Not reported		(25)
65	M	Not reported	3.24 mmol/L =12.98	49 ng/L=5.2		Not reported		(25)
73	M	TCC	12.0	5.7		Not reported	1 month CD	(26)
47	F	AC	20.6	29.9		Not reported	7 months CD	(27)
75	M	SCC	13.0	5.4	34,700	Not reported	4 months CD	(28)
81	M	Sarcomatoid carcinoma	10.5	4.9	16,300	Not reported	5 months CD	(29)
51	M	TCC and partial SCC	11.2	2.0	30,200	98.3	Alive at 40-months postoperative follow-up	(30)
83	M	TCC	13.8	7.1	37,100	Not reported	1 month CD	(31)

PTHrP: parathyroid hormone-related protein, WBC: white blood cell, G-CSF: granulocyte colony-stimulating factor, F: female, M: male, SCC: squamous cell carcinoma, TCC: transitional cell carcinoma, AC: adenocarcinoma, CD: cancer death

bladder cancer has been reported in spinal cord injury patients with recurrent urinary tract infections (17), and we speculate that this patient was also in an environment in which squamous cell carcinoma of the bladder was more likely to develop than chronic cystitis due to prolonged balloon retention from the development of rectovesical disorders caused by Cobb syndrome. Although PTHrP production has been reported in bladder cancer, most cases are from transitional epithelial carcinoma, and this is the fifth case of PTHrP-producing hypercalcemia in squamous cell carcinoma that we found reported (Table 2) (16, 19-31). In bladder cancer, PTHrP production as well as G-CSF production characterized by hyperleukocytosis has been reported (32). Although normal serum G-CSF levels vary across reports, they are generally <30 pg/mL. Our patient's serum G-CSF level was mildly elevated at 36.7 pg/dL. The elevated WBC count on admission may have been due to a paraneoplastic syndrome associated with a G-CSF-producing tumor. This patient's findings were consistent with the reported poor prognosis of G-CSF-producing bladder cancer (33).

Conclusions

To our knowledge, no previous reports have described Cobb syndrome combined with any cancer. The patient in the present case overcame serious complications of a spinal AVM or impending lumbar aortic aneurysm that may have been caused by Cobb syndrome and survived to an advanced age. This is the first case of Cobb syndrome diagnosed as a malignancy-related hypercalcemia caused by metameric cutaneous metastasis of parathyroid hormone-related protein-producing bladder carcinoma with squamous cell differentiation. These findings suggest that, in cases with segmental cutaneous lesions, the presence of a spinal AVM at the same metamere should be evaluated, and the possibility of a SAMS should be considered.

The authors state that they have no Conflict of Interest (COI).

Acknowledgement

The authors would like to thank Genostaff (Tokyo, Japan), for the immunohistochemical examinations.

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