Clinical Case Report

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Malignant melanoma with indiscoverable skin manifestations presenting with paresis and refractory hypercalcemia

A case report

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Abstract

Rationale: Malignant melanoma with indiscoverable skin manifestations is unusual and refractory hypercalcemia with high metabolic signal of the rectum as initial manifestation is very rare.

Patient concerns: We present a case that presented with paresis, nausea, and vomiting.

Diagnoses: Malignant melanoma with spinal metastasis.

Interventions and outcomes: The patient underwent posterior decompression, partial tumor resection, bone cement reconstruction, and internal fixation. The patient's hypercalcemia was controlled and muscle strength was partially recovered. The immunohistochemical stainings showed Melan-A (+), HMB45 (+), s-100 (+), Vimentin (+), and AE1/AE3 (−).

Lessons: We emphasize the necessity of screening potential existence of neoplasms for the patients with hypercalcemia. Surgical treatment is still necessary for patients with spinal metastasis.

Abbreviations: CTLA-4 = cytotoxic T cell lymphocyte-associated antigen 4, MM = malignant melanoma, PTH = parathyroid hormone, PTHrP = parathyroid hormone-related protein, TIH = tumor-induced hypercalcemia.

Keywords: bone metastasis, hypercalcemia, malignant melanoma

1. Introduction

Malignant melanoma (MM) is caused by the highly malignant melanocytes in the skin and other tissues, which accounts for 1% to 3% of all human malignant tumors.[1,2] MM is the common type of malignant tumors with poor prognosis, metastasis, and high fatality rate. MM usually occurs in the skin and mucous membrane around the foot, vulva, and anus. More than 90% primary tumor sites are in the skin and only a small portion is located in the mucous membranes and eyes.[3] The primary site of malignant melanoma has also been reported in the lung, breast, liver, common bile duct, small and large intestine, bone, and bone marrow.[4–9] The clinical manifestations of malignant melanoma are quite different owing to the involved organs.

There are many etiologies associated with hypercalcemia at present. The main cause of hypercalcemia is associated with malignant tumors. Aside from the malignant tumors, many kinds of etiologies still exist, including primary hyperparathyroidism, drug interactions, kidney failure, and so on. In this case report, we report an interesting case of a middle-aged male who was found to be anemic, thrombocytopenia, refractory hypercalcemia, and subsequent PET-CT scan revealed high metabolic signal in the upper rectum. Eventually due to the spinal cord compression, the patient underwent posterior decompression, partial tumor resection, internal fixation on an emergency basis. The postoperative pathology is consistent with malignant melanoma.

2. Case presentation

A 29-year-old Chinese male was admitted to our emergency room presenting with severe pain in the lower right limb, nausea, and vomiting. The patient had a medical history of poliomyelitis. No home medications were taken. Magnetic resonance imaging in local hospital was suggestive of pathological vertebral fracture of T12 and L5. Investigations on admission showed calcium 3.86 mmol/L, serum creatinine 314 μmol/L, urea 21.63 mmol/L and the rest are shown in Table 1. General status: medium nutrition; clear minded, answering correctly, cooperation during examination. A physical examination revealed the dry skin, tenderness of spinal and surrounding soft tissues. There were no abnormal skin manifestations throughout the body. The patient was diagnosed with the high calcium crisis. We treated the patient with fluid infusion, furosemide, and calcitonin in the emergency. Then we invited the endocrinologist and the hematologist for the

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Table 1

Emergency laboratory data.

Variable	Reference range	On admission
Glutamic-pyruvic transaminase (U/L)	0–50	38
Calcium (mmol/L)	2.13–2.70	3.86
Urea nitrogen (mmol/L)	2.78–7.14	21.63
Creatinine (μmol/L)	59–104	314
Kalium (mmol/L)	3.5–5.5	3.9
Natrium (mmol/L)	135–145	132
Albumin (mmol/L)	35–52	38
Parathyroid hormone (pg/ml)	12.8–62.0	6.5
Serum free calcium (pH 7.4) (mmol/L)	1.08–1.28	1.68
CA242 (U/ml)	0–20	12.8
PSA-T (ng/ml)	0–4.00	0.79
AFP (ng/ml)	0–20	1.0
CEA (ng/ml)	0–5	1.26
CA19-9 (U/ml)	0–34	16.0
CA72-4 (U/ml)	0–9.8	0.8
NSE (ng/ml)	0–16.3	37.5
Cyfra211 (ng/ml)	0–3.5	3.61

AFP = alpha fetoprotein; CA19-9 = carbohydrate antigen 19-9; CA242 = carbohydrate antigen 242; CA72-4 = carbohydrate antigen72-4; CEA = carcino-embryonic antigen; Cyfra211 = Human CYFRA21-1 Antigen, cytokeratin 19 fragment; NSE = neuron specific enolase; PSA-T = prostate specific antigen-total

consultation. We conducted specialized tests and bone marrow biopsy on him. The laboratory test results are shown in Table 2. Soon afterwards the patient suffered from recurrent hypercalcemia.

PET-CT scan was performed in this patient to identify the etiology of multiple bone lesions. PET-CT scan of local hospital revealed high metabolic signal in the upper rectum and multiple bone hypermetabolism lesions throughout the body. Considering the patient's symptoms, physical examination, laboratory tests, and imaging studies, the patient was suspected of bone metastasis of rectal cancer.

During the process of waiting for the results of the bone marrow biopsy, he was accompanied with descendent muscle power of left lower limb and constipation. Physical examination showed limited thoracolumbar activity, tenderness and percussion pain of T8, hypoesthesia below the level of the costal margin, muscle strength II for left lower limb, and muscle strength 0 for right lower limb due to poliomyelitis. The patient was re-examined for the thoracic MRI, and MRI of the thoracic spine disclosed abnormal tissue extending posteriorly in the epidural space displacing the spinal cord (Fig. 1). Preoperative preparation of a patient with posterior decompression surgery includes a CBC count, typing and crossmatching of blood, and clotting studies. Laboratory tests suggested that the patient was generally in poor condition. Investigations showed hemoglobin 74 g/L, hematocrit 21%, platelet 67×10^9/L, serum kalium 3.2 mmol/L, calcium 3.29 mmol/L, serum creatinine 179 μmol/L, and urea 11.31 mmol/L. The patient underwent posterior decompression, partial tumor resection, bone cement reconstruction and internal fixation in the emergency room. The surgeons found that the patient's cancellous bone was black during surgery. We considered that the patient might be thought to have a malignant melanoma. The patient was taken to the intensive care unit after surgery.

Table 2

Preoperative laboratory data.

Variable	Reference range	On admission
Glutamic-pyruvic transaminase (U/L)	0–50	31
Calcium (mmol/L)	2.13–2.70	3.71
Urea nitrogen (mmol/L)	2.78–7.14	20.71
Creatinine (μmol/L)	59–104	299
Kalium (mmol/L)	3.5–5.5	4.0
Natrium (mmol/L)	135–145	135
Albumin (mmol/L)	35–52	40
Hemoglobin (g/L)	120–160	74
Hematocrit%	35.0–50.0	21
White cell count (/mm^3)	3.50–9.50	4.91
Platelet (/mm^3)	100–350	67
Alkaline phosphatase (U/L)	45–125	99
Phosphorus (mmol/L)	0.81–1.45	1.51

After transferring to the orthopaedic ward, this patient needed large quantities of platelets as part of treatment with inexplicably decreasing platelets. We had to use a lot of calcitonin to control his refractory hypercalcemia. Besides, we used zoledronic acid injection as a therapeutic alternative in the pain relief for him until his renal function recovered. The patient's hypercalcemia was effectively controlled. The results of bone marrow biopsy (Fig. 2) in posterior hematology showed that some bone and bone marrow tissues were infiltrated by a large number of heteromorphic cells. The immunohistochemical stainings showed Melan-A (+), HMB45 (+), s-100 (+), Vimentin (+), and AE1/AE3 (−). Subsequently, metastatic malignant melanoma of T8 was proved by pathology (Fig. 3). The muscular strength of left lower limbs had completely recovered. The thoracic X-ray indicated that the internal fixation position was suitable (Fig. 4). The patient ultimately went to the oncology department for further treatment.

3. Discussion

This is a case of a 56-year-old man who presented with bone pain, nausea, vomiting, and refractory hypercalcemia. Bone metastasis of rectal cancer was suspected according to the results of PET-CT. However, this patient was eventually diagnosed as malignant melanoma with indiscoverable skin manifestation. We could draw on experiences from this rare case.

The causes of hypercalcemia can be divided into PTH-mediated and non-PTH-mediated conditions. PTH-mediated hypercalcemia include primary hyperparathyroidism, tertiary hyperparathyroidism, parathyroid carcinoma, etc., whereas non-PTH-mediated hypercalcemia could result from endocrine diseases, intake of certain drugs, malignancy, renal failure, and vitamin D-associated hypercalcemia.[10] Primary hyperparathyroidism and cancer-associated hypercalcemia are the most frequent causes of hypercalcemia.

Tumor-induced hypercalcemia (TIH) has been reported to occur in 10–15% of patients with advanced cancer and can be observed in any type of tumor.[11] Of note, physicians in charge of non-cancer patients presenting with hypercalcemia should not neglect the potential existence of neoplasm. The malignancy-related hypercalcemia could be attributed to the following mechanisms:

(1) Humoral hypercalcemia mediated by parathyroid hormone-related peptide (PTHrP), which commonly occurs in squamous cell carcinoma.
(2) Local osteolytic hypercalcemia in the patients with extensive bone metastases, which could be often found in multiple myeloma and breast cancer. The proposed mechanisms include direct bone destruction, as well as the release of cytokines which lead to osteoclast activation.

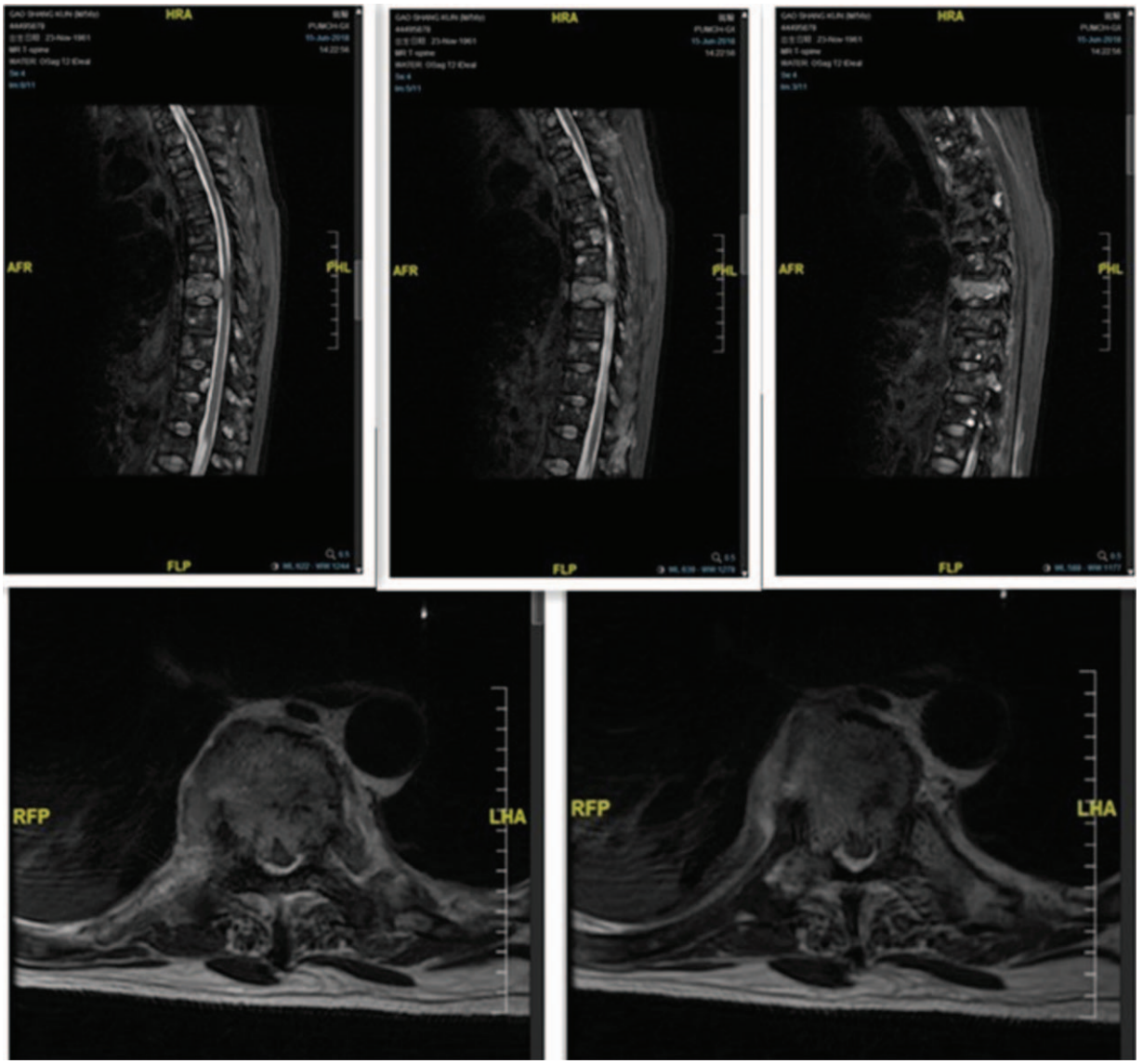

Figure 1. Thoracic MRI showed severe damage of T8 vertebrae and compression of the spinal cord.

(3) Other mechanisms, including extrarenal production of vitamin D, and primary or ectopic secretion of PTH.[12]

First, osteolysis caused by bone metastasis in malignant tumors, such as breast cancer and renal cell carcinomas; Second, multiple myeloma and other hematologic malignancies which affect the bone marrow. Besides, some malignant tumor of the lung, kidney, urogenital system can synthesize and secrete cytokines and tumor-related hormones, such as, IL-6, IL-1, and parathyroid hormone-related protein (PTHrP). In addition, some granulomatous tumors can cause hypercalcemia, including sarcoidosis, tuberculosis, leprosy, and histoplasmosis.[13–16]

As for treatment regimens, identifying the etiology and treating the primary disease is the most fundamental and effective way to control hypercalcemia.[12] Hydration is critical, since the patients with hypercalcemia are generally volume depleted. Caution is needed to avoid fluid overload for the patients with cardiac or renal insufficiency. The efficacy of diuresis has been found to be limited. More importantly, bisphosphonates are one of the most effective drugs for cancer-related hypercalcemia, through blocking the bone resorption in osteoclasts to decrease blood calcium. The main side effect of diphosphate is kidney impairment, so diphosphate is contraindicated in patients with renal insufficiency. The serum creatinine of the patient in this case is 179 μmol/L. Hence, diphosphate is not allowed in the course of medical treatment. Calcitonin is also an effective and frequently-used drug for hypercalcemia, and when combined with bisphosphonates, blood calcium can decrease more rapidly and substantially. Denosumab and calcimimetics such as Cinacalcet are a novel class of drugs used in human medicine that target the Ca receptor and inhibit the secretion of PTH.[17,18] In addition, dialysis is a treatment option for high calcium crisis or refractory hypercalcemia.

Recently, the incidence and mortality of melanoma have been increasing rapidly in China.[19] The primary site of more than 90% malignant melanoma is skin, with a small portion in the hair and eyes.[20] In this case, perplexingly, PET-CT shows the high metabolic signal in the upper rectum without skin manifestation. Traditional treatment regimens were less effective for the patients

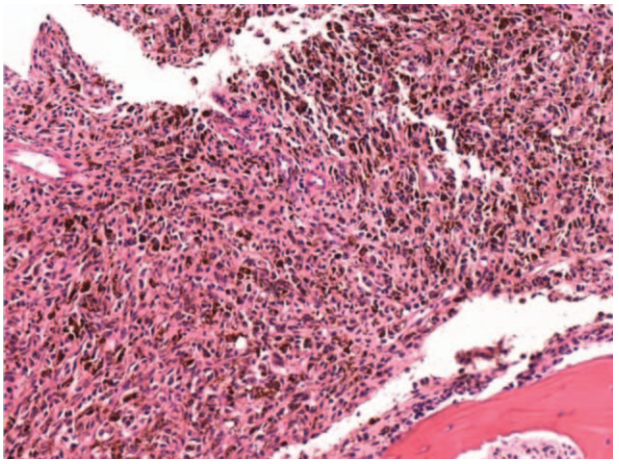

Figure 2. Pathology from posterior iliac showing a small number of bone and bone marrow tissues infiltrated with a large number of heteromorphic cells, accompanied by pigmentation. Immunohistochemistry: Melan-A (+), HMB45 (+), S-100 (+), Vimentin (+), AE1/AE3 (−), CD3 (+), CD20 (+), CD15 (+), MPO (+).

with advanced malignant melanoma, until the development of targeted therapy and immunotherapy, which revolutionized the management for the patients with advanced disease.[21] The specific targeted treatment of malignant melanoma selectively inhibit the MAPK/ERK (RAS-RAF-MEK-ERK) signaling pathway, including BRAF (V600E/K) inhibitors, c-kit inhibitors, and NRAS inhibitors.[22,23] Immunotherapy targeting cytotoxic T cell lymphocyte-associated antigen 4 (CTLA-4) and programmed cell death 1 (PD-1) has also been proven effective for malignant melanoma.[21]

Distant metastasis and poor prognosis are the clinical features of malignant melanoma. The primary site usually transfers to the bone tissue through blood stream and lymphatic metastasis. The bone metastases of malignant melanoma usually occur in the vertebrae. The patient in our case was definitely diagnosed with bone metastasis of malignant melanoma. Bone tissue is a common site for distant metastasis of malignant tumors, besides lung and liver. Generally, spine is the most frequently involved metastatic sites for malignant tumors, followed by rib and pelvis.[24] Early bone metastases are usually asymptomatic, while lesions of the skeleton can be found by isotope bone scan. The major skeletal complications associated with bone metastases include: cancer-induced bone pain, hypercalcemia, pathological bone fractures, metastatic epidural spinal cord compression, and cancer cachexia.[25] The pain symptoms are initial and important. However, the co-morbidity of lumbar disc herniation often leads

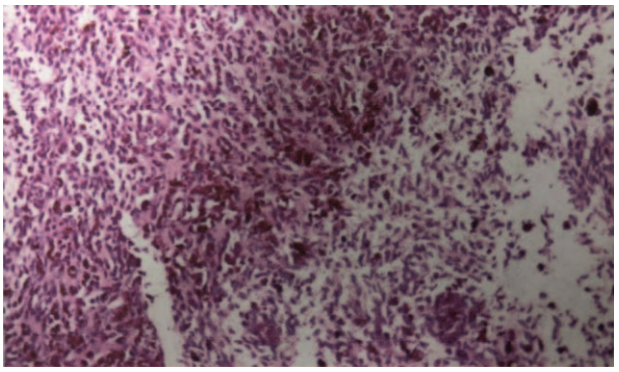

Figure 3. Pathology from T8 showing the lesion was consistent with metastatic melanoma. Immunohistochemistry: B-raf (−), Ki-67 (index 60%), Melan-A (−), HMB45 (+), SOX10 (−), S-100 (+).

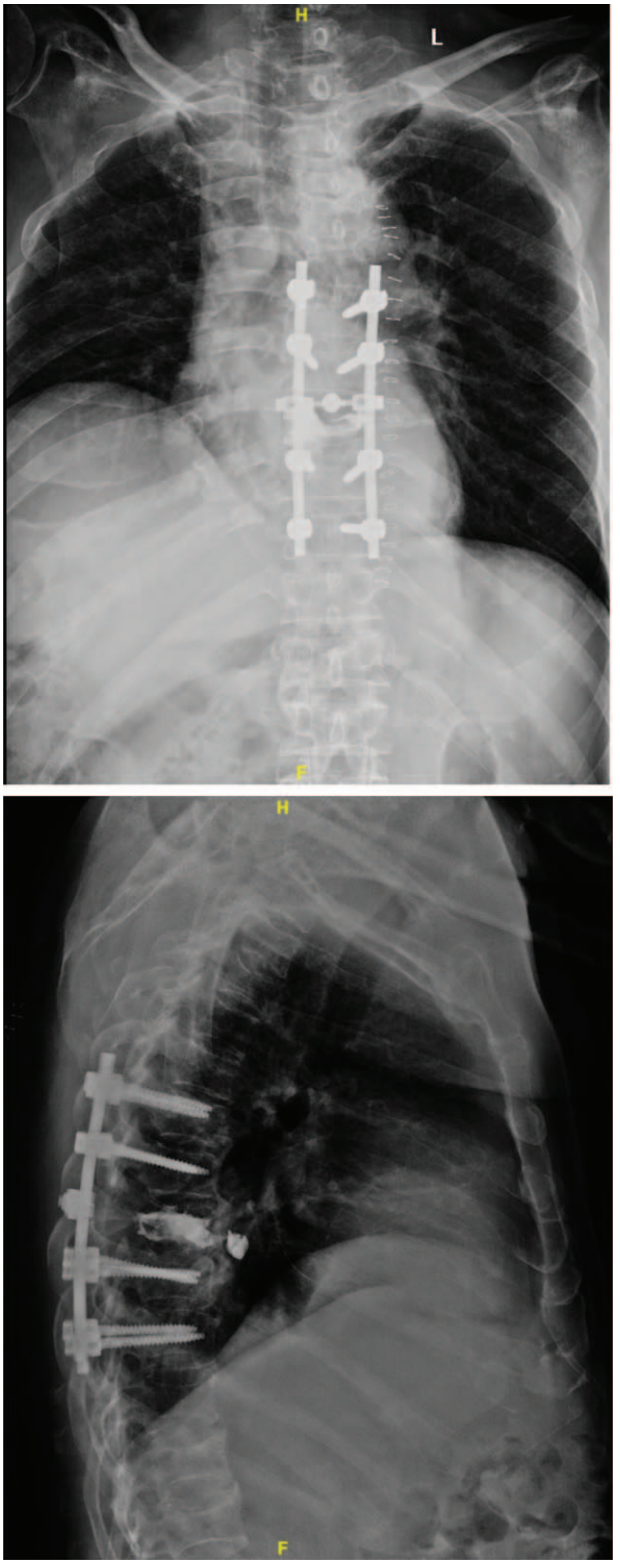

Figure 4. Spine PA & LAT showing the position of thoracic internal fixation is suitable.

to the delay of diagnosis and treatment of bone metastasis. Hypercalcemia is not uncommon in patients with bone metastatic carcinoma. Bisphosphonate is currently recognized as effective drugs that can treat bone metastatic carcinoma and control its related complication. The patient underwent posterior decompression, partial tumor resection, bone cement reconstruction and internal fixation for spinal compression caused by malignant tumor. Currently, better surgical treatment for spinal metastasis has been triggered by improved surgical techniques.[26] We intend to use the surgical interventions to relieve pain, reduce local tumor, stabilize spine, and preserve the neurological function. Molina et al has indicated that the survival rates for patients with spinal metastasis were improved with progressive surgical techniques. For patients with spinal metastasis, surgical treatment is still necessary.[27]

4. Conclusion

Along with sorting out its causes of hypercalcemia in emergency departments, surgeons in charge of non-cancer patients presenting with hypercalcemia often neglect the neoplastic causes of hypercalcemia. Here, we presented an interesting case of hypercalcemia along with vertebral lesions and high metabolic signal in the upper rectum, which was eventually diagnosed of bone metastasis of malignant melanoma with indiscoverable skin manifestations. We emphasize the necessity of screening potential existence of neoplasms for the patients with hypercalcemia, as well as the importance of mastering the management of hypercalcemia as a surgeon.

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Author contributions

Data curation: Xi Zhou.
Formal analysis: Xi Zhou.
Resources: Pei-pei Wang, Xi Chen.
Supervision: Yong Liu.
Validation: Yong Liu.
Writing – original draft: Pei-pei Wang.
Writing – review & editing: Li-wen Wang.

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