



# Cerebral metastases of parathyroid carcinoma: a case report and literature review

Yanan Li<sup>1,2</sup>, Anjun Zuo<sup>3</sup>, Ling Wei<sup>4</sup>, Fangjie Xin<sup>1</sup>, Weiwei Fu<sup>1#</sup>, Peng Zhao<sup>1#</sup>

<sup>1</sup>Department of Pathology, the Affiliated Hospital of Qingdao University, Qingdao 266000, China; <sup>2</sup>Department of Clinical Medicine, School of Clinical Medicine, Qingdao University, Qingdao 266000, China; <sup>3</sup>Department of Surgery, <sup>4</sup>Department of Neurology, the Affiliated Hospital of Qingdao University, Qingdao 266000, China

#These authors contributed equally to this work.

Correspondence to: Peng Zhao; Weiwei Fu. Department of Pathology, the Affiliated Hospital of Qingdao University, Qingdao 266000, China.

Email: qzhaopeng@sina.com; eer-df@163.com.

**Abstract:** Parathyroid carcinoma (PC) is an uncommon endocrine tumor. At first presentation, the diagnosis of PC by morphologic analysis is challenging. Indeed, approximately 50% of metastatic PCs were categorized as benign at the time of first resections. However, single brain metastasis rarely occurs in PC patients and could represent a further obstacle for PC diagnosis in the absence of other symptoms. The present report describes the clinicopathological features of a case of PC intracranial metastases in a 60-year-old woman, who presented space-brain occupying symptoms as a first manifestation. To the best of our knowledge, only ten cases with brain metastasis were reported in the literature.

**Keywords:** Parathyroid carcinoma (PC); metastasis; intracranial; pathology; diagnosis

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## Background

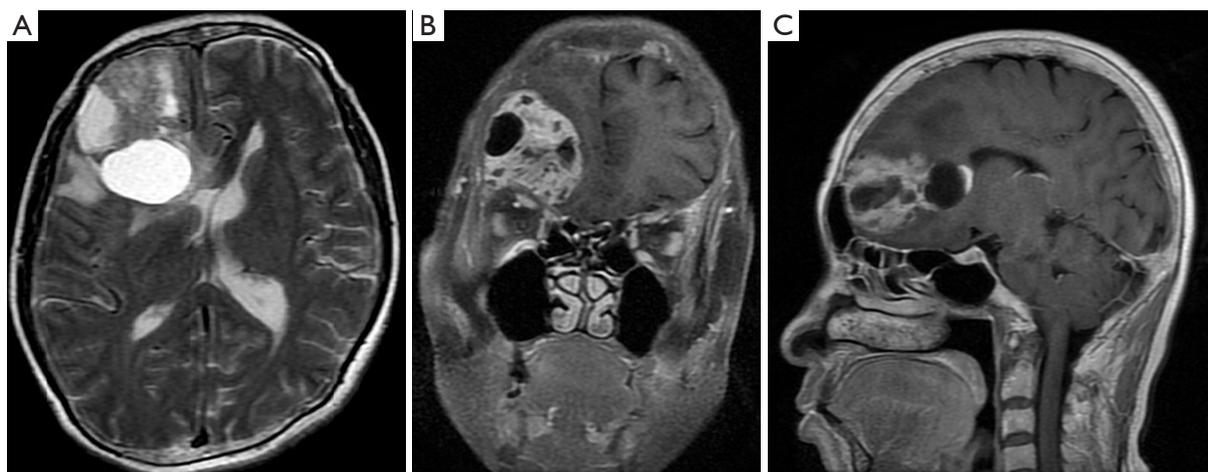
As a rare endocrine tumor, parathyroid carcinoma (PC) accounts for 1% of parathyroid gland tumors and less than 1% of primary hyperparathyroidism (PHPT) (1). The typical PC histology shows that tumor cells are arranged in nests and separated by thin fibrous bands with multiple thin-walled capillaries (2). PC clinical manifestations are dominated by an excessive secretion of parathormone [human parathyroid hormone (PTH)] with symptoms ranging from none to severe hypercalcemia, or parathyrotoxicosis, usually including bone pain, pathological fractures, urinary stones, hematuria, or peptic ulcers (3).

Among metastatic PC cases, more than 25% were reported to involve lungs, but occasionally also involve the bones, liver, pleura, or pancreas (4). PCs intracranial metastases are extremely rare. For those patients presented in the emergency department, for brain occupying symptoms and without a cancer history, the diagnosis remains a challenge for the clinicians due to the limited

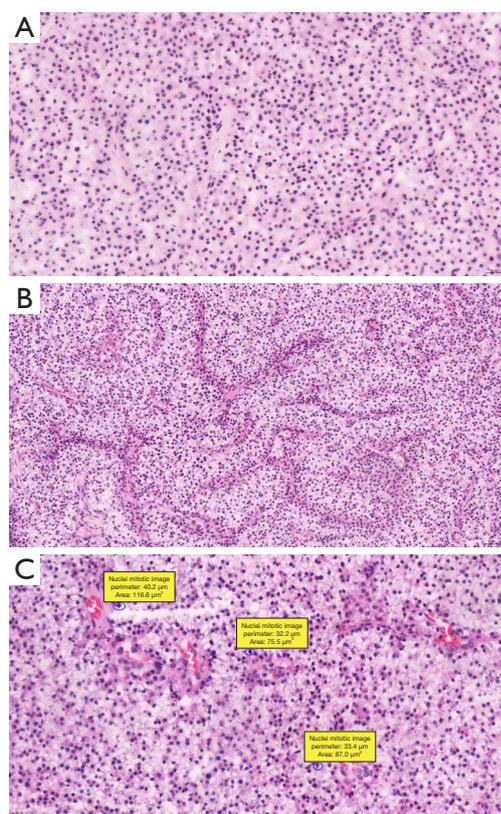
clinical information. In this study, we report one of these rare cases.

## Case presentation

On May 23, 2018, a 60-year-old woman, with no cancer history, presented at the emergency department with headache, nausea and vomiting. Using computed tomography (CT) scan analysis, at the local hospital, we identified an evident mass in the right frontal lobe of the brain. Since PC was not initially suspected, only limited laboratory tests were performed. The patient calcium blood level, analyzed by gas analysis, was 1.75 mmol/L (our reference interval: 1.15–1.29 mmol/L). The patient chest X-ray showed that the soft tissue density, at the upper end of the esophagus, was approximately 31 mm × 21 mm at maximum dimension. A contrast-enhanced CT scan and a magnetic resonance imaging (MRI) of the head confirmed the lesion at the right frontal lobe and showed the presence of surrounding oedema, a mass effect and a solid mixed cyst,



**Figure 1** Brain CT and MRI show a tumor at the right frontal, with oedematous surroundings. CT, computed tomography; MRI, magnetic resonance imaging.



**Figure 2** Microscopic morphology under HE staining. (A) Shows a frozen section with magnification of  $\times 400$ ; (B,C) show conventional HE sections with magnifications of  $\times 200$  and  $\times 400$ . The tumor cells had uniform and clear cytoplasm and round mitotic nuclei. Interstitial blood vessels are abundant.

measuring 53 mm  $\times$  40 mm at the maximum dimension (*Figure 1*). The patient underwent tumor resection on May 28 and discharged after one week. On May 2019, the subject went to their local hospital and resected the primary lesion. The serum calcium and PTH levels were 2.70 mmol/L (our reference interval: 2.15–2.57 mmol/L) and 458.3 pg/mL (our reference interval: 12–88 pg/mL), respectively. The postoperative pathology analysis confirmed the diagnosis of PC. Indeed, the patient's serum PTH and calcium levels returned towards baselines after tumor resection.

## Investigation

### *Morpho-pathological analysis*

The cross-examination of the brain lesion demonstrated the presence of a grayish solid mass, measuring 6.0 $\times$ 3.5 $\times$ 2.5 cm<sup>3</sup>. Both frozen and unfrozen resected specimens were processed in 10% neutral-buffered formalin fixation, paraffin embedded, sectioned and stained with hematoxylin and eosin (HE). A microscopic examination demonstrated that the tumor was composed of relatively consistent cells, which were organized in nests and separated by thin fibrous bands and abundant blood vessels. Most tumor cells had ample and clear, or faint eosinophilic cytoplasm with a round to ovoid nuclei, containing dense chromatin and inconspicuous nucleoli. We registered 5 mitoses per ten high power fields, and no capsular or probable vascular space invasions, were detected (*Figure 2*). In the second

surgical specimen, the tumors demonstrated irregular cell nests of vacuolated and clear neuroendocrine cells. These tumor cells had abundant and clear, or eosinophilic cytoplasm, with rounded nuclei and low mitotic activity. The morpho-pathological analysis reveals similarities between the two specimens of the two resections.

### Immunohistochemistry

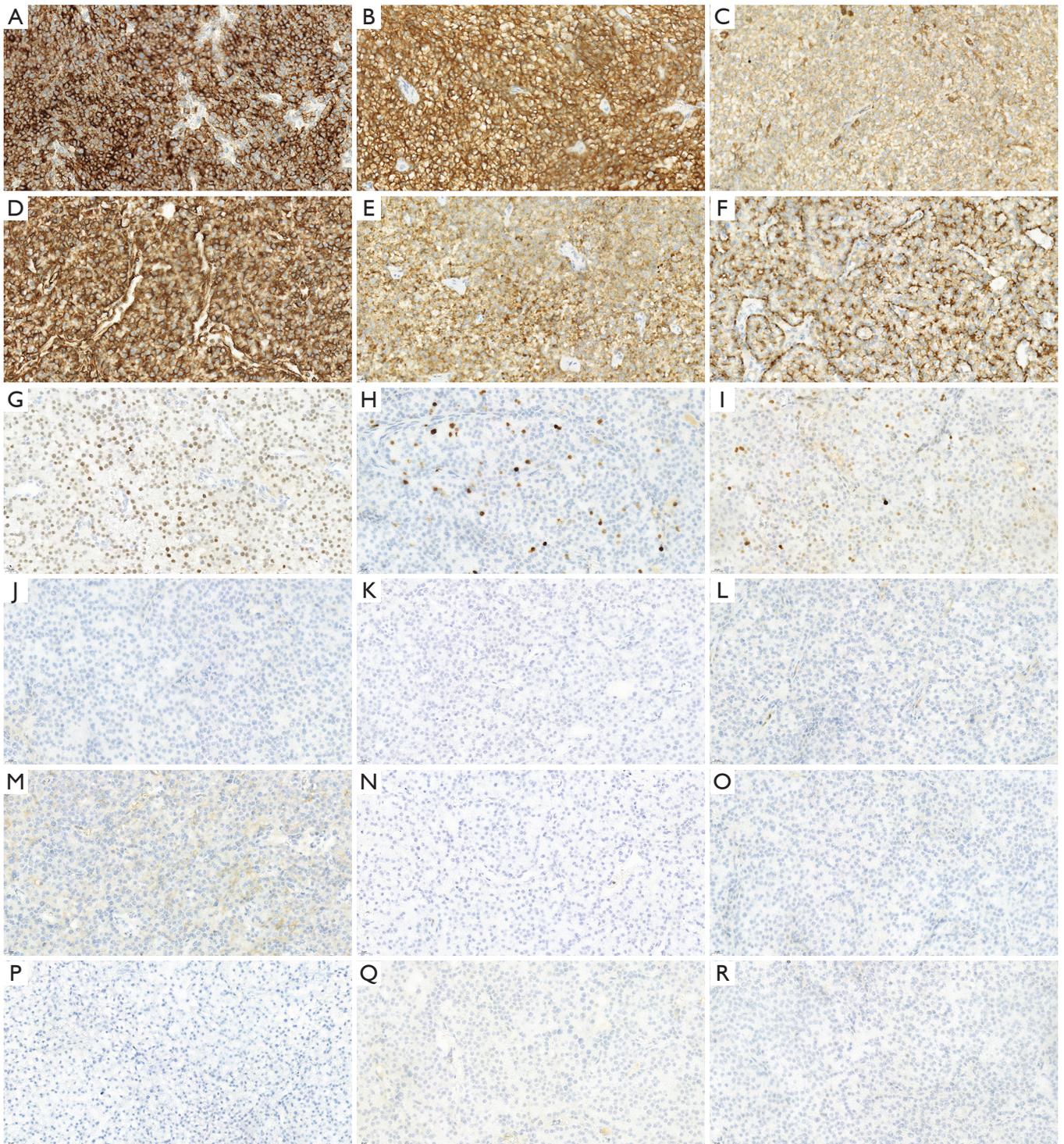
The EnVision method was used on the 5  $\mu$ m paraffin-embedded tissue sections. In brief, the sections were preprocessed in 10 mM citrate buffer solution (pH 6.0), treated with 0.3% hydrogen peroxide in methanol for 30 min, and subsequently washed in phosphate-buffered saline. Then, the sections were incubated overnight at 4 °C with the following antibodies: PTH [working solution (WS), ZM-0268, Roche], oligodendrocyte transcription factor 2 (OLIG2; WS, ZA-0561, Roche), antigen Ki67 (KI67; WS, ZA-0187, Roche), glial fibrillary acidic protein (GFAP; WS, ZA-0529, Roche), paired-box gene 8 (PAX8; WS, ZM-0468, Roche), carbonic anhydrase 9 (CA9; WS, ZM-0161, Roche), endothelial transcription factor 3 (GATA3; WS, ZA-0661, Roche), alpha-methylacyl coenzyme A racemase (AMACR; WS, ZM-0227, Roche), synaptophysin (SYN; WS, ZM-0246, Roche), chromogranin-A (CHGA; WS, ZM-076, Roche), S-100 proteins (S-100; WS, ZA-0225, Roche), vimentin (Vimentin; WS, ZA-0511, Roche), spectrum of cellular keratin (CK-PAN; WS, ZM-0069, Roche), common acute lymphoblastic leukemia antigen (CALLA; WS, ZA-0526, Roche), epithelial membrane antigen (EMA; WS, Kit-0011, Roche), Caudal-related Homeobox Transcription Factor 2 (CDX-2; WS, RMA-0631, Roche), somatostatin receptor 2 (SSTR2; WS, ZA-0578, Roche), thyroid transcription factor-1 (TTF-1; WS, ZM-0270, Roche). After washing excess antibodies, hybridizations with corresponding secondary antibodies (Roche, Germany) were performed for 20 min at 37 °C and hematoxylin or DAB (WS, Kit-0014) staining was applied. Immunohistochemistry demonstrated that the tumor cells were positive for GATA3, PTH, CK-PAN, Vimentin, SYN, PAX-8, CA9, CHGA and AMACR, but negative for CALLA, OLIG2, SSTR2, S100, GFAP, EMA, TTF-1 and CDX-2. The proliferation index using Ki 67 showed an approximately 10 % positivity in the tumor cells, p53 shows about 20% (Figure 3). The results of immunohistochemistry of the second surgical specimen showed similar results.

### Discussion

PCs are rarely non-functional and their main clinical manifestations include hyperparathyroidism, or hypercalcemia. PCs grow slowly, and at early stages, lack typical symptoms. The physical examination exhibits a palpable neck mass in 30 to 75% of PC patients. Approximately 50% of patients relapse within three years after diagnosis. In this report, we describe a case of a 60-year-old woman presented with brain metastasis originated from a PC, who solely presented symptoms of a space-occupying lesion of the brain. Although one-third of PC patients have metastases, intracranial metastases rarely occur, and only 10 cases were previously reported (Table 1) (1,2,4-12). In those cases, the mean age at diagnosis, was 55 years (range, 27–61 years) regardless of gender. Only one case displayed a single metastasis to the brain; whereas, the others showed multi-organ metastases, encompassing lungs, and/or lymph nodes. In the reported case, the primary lesion was impalpable, and the brain occupying symptoms were the main manifestation.

Most PCs display abundant band-forming fibrosis, with multiple thin-walled capillaries, tumor cells with dense chromatin, and mitosis that can be found in 50% of malignant tumors, which usually contain  $\geq 5$  mitoses per 10 high power fields. In this case, some tumor cells were arranged in nests, mitoses were frequent, but fibrous cords were not seen. The diagnosis of malignancy should be restricted to tumors, with evidence of invasive growth involving adjacent structures, such as capsular and/or extracapsular blood vessels, or perineural spaces and/or those with documented metastases (13).

Morphologically, PCs could resemble other endocrine tumors, such as pituitary carcinoma, metastases of well-differentiated neuroendocrine tumors of the gastrointestinal tract or lung, and metastases of the renal cell carcinoma. Immunohistochemistry contributes in distinguishing these tumors, since the positivity to CHGA, SYP and CD56, and most importantly to PTH and GATA3, are characteristic of PCs. Recently, Yu *et al.* showed that PTH and CHGA are useful markers for the diagnosis of parathyroid neoplasms; while, SYP and INSM1 lack sensitivity (14). A parathyroid tumor is usually positive for PAX8, GATA3, and OLIG2 (14,15). In the absence of PHPT symptoms, PC is difficult to diagnose by radiology. In fact, in the present case, the diagnostic options initially included glioma, metastasis of unknown origin, and meningioma.



**Figure 3** The immunohistochemical staining of the tumor shows a strong positivity for PTH, SYN, CHGA, VIMENTIN, AMACR and CK, and a partial positivity for GATA3. The positive rate of Ki67 was approximately 10%, P53 is about 20%. OLIG2, P53, PAX8, SSTR2, CA9, CALLA, EMA, GFAP, CDX-2 and TTF-1 were negatively expressed (original magnification 400×).

**Table 1** Reported cases of intracerebral metastasis of parathyroid carcinoma

No.	Age, sex	Serum calcium at presentation (mg/dL)	PTH at presentation (pg/mL)	Sites of metastases	Location in the brain	Survival after diagnosis of HPT (months)	Survival after diagnosis of intracranial metastasis (months)	Author, year
1	27, M	9.2-9.8	NR	Lymph nodes, lung, brain	NR	27	58	Aldinger <i>et al.</i> , 1982
2	45, M	12.9	NR	Lymph nodes, lung, brain	Right occipital lobe	117 (alive)	5 (alive)	Yamamoto <i>et al.</i> , 1996
3	44, M	15.2	467	Brain	Left parasagittal front parietal	61	13	Tyler <i>et al.</i> , 2001
4	45, F	NR	NR	Lung, brain	The sellar region	45	31	Eurelings <i>et al.</i> , 2002
5	35, F	17.8	NR	Lung, brain	Multiple	38	0	Kar <i>et al.</i> , 2003
6	54, F	10.76	271	Lymph nodes, lung, brain	Right frontal lobe	29	8	Kern <i>et al.</i> , 2004
7	61, F	13.2	730	Lung, brain	Right frontal lobe	19	6	Yoshida <i>et al.</i> , 2006
8	49, M	15.2	475	Lymph nodes, lung, brain, bone	Left cerebellar	1	0	Barker <i>et al.</i> , 2014
9	62, F	11.1	37	Lymph nodes, lung, brain, right orbit	multiple in both hemispheres	18	2	Studentova <i>et al.</i> , 2015
10	49, M	22.3	3,560.7	Thyroid, lung, brain, surrounding soft tissue	Multiple in left occipital lobe	4	4	Sadacharan <i>et al.</i> , 2017
11	80, F	7	NR	Brain, bone	Right frontal lobe	12 (alive)	12 (alive)	Current report

Note: the patient's survival time was as reported in the article. NR, not reported.

The etiology of PC is largely unknown; however, it has been reported in Hyperparathyroidism-jaw tumors (HPT-JT), a rare autosomal syndrome in which the incidence of PC is around 15%. Mutations of the CDC73 gene are strongly associated with the HPT-JT syndrome, HPT-JT-related PC, and with 70% of sporadic PCs (16). CDC73 gene locates at the chromosome locus 1q31, and encodes a protein involved in transcriptional and post-transcriptional regulations (17). PHPT is the first and most common manifestation of the HPT-JT syndrome and frequently involves a single parathyroid gland. The high incidence of PC is a characteristic of familial HPT-JT. This tumor has a larger size, white color, adherence to adjacent tissues, and firm consistency (18).

The gold standard therapy of PC is the en bloc resection of the primary tumor by performing a parathyroidectomy together with ipsilateral thyroid lobectomy. The whole tumor resection significantly improves long-term survival of PC patients. The postoperative management of the patients includes the monitoring of the serum calcium

level. For multiple metastatic lesions, the long-term survival is compromised; hence, the reduced sensibility to chemotherapy and radiotherapy of the PC metastasis (19). In the present case, after the resection of the brain metastasis, the primary lesion surgery was performed in the absence of other metastases.

To conclude, this article reported a case of an intracranial metastasis originated from a PC in a 60-year-old female who displayed symptoms of space-occupying brain lesion, without the classic PHPT signs, derived from PC. Therefore, patients in whom brain masses are observed, PC should be considered in the differential diagnosis.

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## Footnote

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/tcr.2020.01.66>). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. A written informed consent and any accompanying images were obtained from the patient for publication of this Case report.

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