Brain metastases from differentiated thyroid cancer occurring during and after radioactive iodine therapy: a report of four cases and literature review

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Research

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Abstract

Background Brain metastases from differentiated thyroid cancer are uncommon, and the prognosis of patients with them is poor. To explore the optimal treatment for this entity, we retrospectively investigated incidence and features of brain metastases from differentiated thyroid cancer that appeared during and after radioactive iodine therapy. Methods Between 2002 and 2012, 89 patients of differentiated thyroid cancer were included (median age, 63-years; male/female = 29/60). The median follow-up time from first ablation was 63 months (range: 1–175 months). The median cumulative radioactive iodine dose was 8.51 GBq (range: 1.11–42.55 GBq). Results During the follow-up, brain metastases occurred in four (4.5 %) patients. The median follow-up time after first ablation of four patients was 69 months (22, 63, 76 and 105 months). They had already had extracranial metastases at first ablation (lung metastases: 3, lung and bone metastases: 1), and had one or more lesions resistant to radioactive iodine therapy at diagnosis of brain metastasis. Three of them had experienced major hemorrhage from brain metastasis. Survival time intervals from the diagnosis to brain metastasis were 2.5, 3.6, 13 and 13.1 months. Conclusion Brain metastases of differentiated thyroid cancer were relatively uncommon. Prognosis of patients with brain metastasis was unfavorable because of frequent major brain hemorrhage and frequent existence of concomitant extracranial lesions resistant to radioactive iodine therapy. To prevent intracranial hemorrhage, early treatment seemed to be necessary for brain metastases from differentiated thyroid cancer.

Introduction

Differentiated thyroid cancer (DTC) patients are expected to have long-term survival [1]. Even in patients with distant metastases, radioactive iodine (RAI) therapy after total thyroidectomy leads to long-term survival [2–4]. However, once brain metastasis (BM) occurs, the prognosis is poor [5]. According to the previous report, incidence of BM from thyroid cancer is approximately 1% of all patients with thyroid cancer [5]. As BMs from DTC is uncommon, prognosis in patients with BMs from DTC, which appear during and after repeated RAI therapy, is not well investigated. We retrospectively investigated the incidence and features of BM from DTC that occurred during and after RAI.

Materials And Methods

Between 2002 and 2012, 98 patients of DTC received RAI in our institution. We excluded 9 patients whose histological subtype was unknown because the initial surgical treatment was performed long ago at other institutions. Finally, 89 DTC patients were included. The median patient age at first ablation was 63 years (range: 13–84 years), and male/female ratio was 29/60 (Table 1). Histological analysis of primary tumor was revealed papillary thyroid carcinoma (PTC) in 80 (89.9%) patients, PTC-follicular variant in 2 (2.2%) patients, and follicular thyroid carcinoma (FTC) in 7 (7.9%) patients. The median follow-up time from first RAI treatment was 63 months (range: 0.1–175.3 months). The median cumulative RAI dose was 8.51 GBq (range: 1.11–42.55 GBq), and the median cumulative RAI time was three times (range: 1–12 times). Among them, 44 patients had metastases at first RAI treatment (Lung 39, bone 2 and lung and

bone 3). We retrospectively investigated clinical features of BMs. Protocol of the study was approved by our institutional review board. The 5-year incidence of BM was calculated using the Kaplan-Meier method. The survival rates were analyzed using the Kaplan-Meier method and the log-rank test. Statistical analyses were performed using JMP software (version 12.0; SAS Institute Inc, Cary, NC).

Results

A total of four (4.5%) patients were diagnosed with BM during or after RAI therapy, confirmed by computed tomography (CT) or magnetic resonance imaging (MRI). The 5-year incidence of BM was 3.5% (Fig. 1a). The follow-up period from first RAI therapy of these four patients was 22, 63, 76, and 105 months, respectively. Among the patients with distant metastases at first ablation, the 5-year incidence of BMs was 6.5%.

Clinical characteristics of patients with BMs were presented in Table 2. All of the four patients had PTC and extracranial metastases at the first RAI therapy (lung, 3; lung and bone, 1). The median cumulative doses of RAI therapy were 17.76 GBq (range: 8.51–27.01 GBq). All patients had one or more RAI-refractory lesions when BMs occurred. Three patients had solitary BM and one patient had two BMs. Regarding the size of BM at diagnosis, the maximum diameter ranged from 12 to 40 mm for the four measurable BMs, and another BM could not be measured due to hemorrhage. The interval from initial surgical treatment of DTC to BM was varied from 2.5 to 21 years. Median thyroglobulin level at diagnosis of BM was 622 ng/mL (range: 80.2–2,082 ng/mL, normal range $\leq$ 33.7 ng/mL). Except for one patient who received surgery and postoperative whole brain radiotherapy (WBRT) of 37.5 Gy immediately after diagnosis of BM, all patients experienced major hemorrhage from BMs. Intervals from diagnosis of BM to hemorrhage was simultaneous, 1.0, and 3.6 months, respectively. The survival times from diagnosis of BM were 2.5, 3.6, 13.0 and 13.1 months. The prognosis of patients with BMs was poor, i.e., worse than those (n = 85) without BMs (Fig. 1b, $P < 0.001$).

Discussion

BMs of DTC have been reported as a rare condition. In our study, BMs appeared in 4.5% (4/89) of patients during or after RAI therapy. Slutzky-Shraga et al. reported that the frequency of BMs was higher (appropriately 6%) in patients with distant metastases of non-medullary thyroid cancer [6]. In our study, when limited to the patients with distant metastases at first ablation, the incidence of BMs was 9.1%. Therefore, the brain is a relatively frequent site of distant metastases following lung and bone.

McWilliams et al. reported that 85% of the thyroid cancer with brain metastasis died of extracranial diseases in their 16 patients [7]. Among our cases, three of four patients experienced massive hemorrhage from BMs (Fig. 2, 3). According to previous reports of BMs from hypervascular tumors such as hepatocellular carcinoma, melanoma, and renal cell carcinoma, they tend to cause brain hemorrhage [8–10]. BMs from thyroid cancer are known to be hypervascular; therefore, it may cause bleeding like other hypervascular brain metastases. To the best of our knowledge, there have been five case reports of

hemorrhagic BMs to date; they are summarized in Table 3 [11–14]. In these case reports, the size of BMs with hemorrhage was greater than or equal to 30 mm. In our present study, 12 mm and 23 mm BMs caused bleeding. We should be careful about hemorrhages even if the size is small. Furthermore, based on previous reports and our present study, the number of BMs that cause bleeding from DTC is often small [15]. For patients with solitary BMs of DTC, since incidence of intracranial hemorrhage from BMs is high, immediate aggressive local treatment such as surgical resection should be considered [7].

Although it has been reported that the intervals from diagnosis of thyroid cancer to BM development were reported to be 3.8–6.4 years [5,7,15], appearances of BMs after more than 10 years after initial diagnosis are not rare [9]. In this study, one patient experienced BM 20 years after initial diagnosis of DTC. Because BMs of DTC are uncommon, the risk of bleeding from them has not been well considered on follow-up imaging studies. It has been reported that lung or bone metastases precede BMs [6]. In our study, extracranial metastases (lung or bone) preceded BMs in all cases. Based on our study, the risk of BMs and intracranial hemorrhage from BMs should be considered when extracranial metastases become to be resistant to repeated RAI therapy.

The prognosis of patients with BMs of thyroid cancer is poor. It has reported that the median survival time of patients with BMs of thyroid cancer ranged from 2.6 to 4.7 months when treatment was not performed [5–7,15]. One of the causes of this outcome may be related to the nature of BMs in thyroid cancer, which have a tendency to bleed. There is no clear standard treatment of BMs of DTC as they are rare. However, surgical resection has been reported to improve prognosis. McWilliams et al. reported that the average survival for patients with surgical treatment was 20.8 months [7]. In our study, two patients with BMs received surgical treatment. The two patients died of extracranial metastases. In one patient, a BM was controlled by surgical resection and WBRT. McWilliams et al. reported that they performed WBRT with or without boost to the tumor bed at doses ranging from 30–54 Gy over 10–30 treatments, the overall survival was 9.5 months (range: 1.6–21.6 months). Salvati et al. reported that the survival average of patients who had solitary BMs of DTC and received surgical resection followed by WBRT (45 Gy) was 19.8 months [16].

Stereotactic radiosurgery (SRS) is also used for limited number of BMs of DTC. Choi et al. reported that the median survival rate for patients who underwent SRS was better than patients who underwent neither surgical resection nor SRS (30.7 months vs. 5 months), ranges of survival period of five patients treated by SRS were 8.8–109 months [15]. SRS might be a treatment option for solitary or small number of BMs.

RAI therapy is often performed for patients with metastases. However, it was reported that only 17% of BMs showed RAI uptake, even when RAI accumulated in other extracranial lesions [5,17]. Moreover, these BMs progressed after RAI therapy despite RAI uptake [7]. Based on these literatures, RAI seemed to be ineffective in majority of BMs of DTC. The clinical course of patients with BMs of DTC is sometimes similar with those of more aggressive histology including poorly differentiated carcinoma or anaplastic carcinoma [5,11]. In our case of surgical resection, the histological findings of BMs indicated poorly

differentiated carcinoma. The very rapid clinical course of this patient suggests that DTC dedifferentiation may have occurred in this patient.

Recently, lenvatinib, which is an oral-intake multi-targeted tyrosine kinase inhibitor, is used to improve progression-free survival time among patients with RAI-refractory thyroid cancer [18]. However, it has been reported that during lenvatinib treatment, there is a risk of major bleeding from the tumor and/or sites of tumor invasion, and also from BMs [19,20]. From this point of view, the use of lenvatinib for BMs should carefully be considered.

This study has some limitations. First, this is a single institutional retrospective study, with a limited number of patients experiencing BM. Second, BM pathology was not revealed except in one patient.

Conclusion

We reported four cases of BMs from DTC who were diagnosed during or after RAI therapy. The 5-year incidence of BM was 3.5%. The prognosis of patients with BMs was poor and significantly worse than for those without BMs. Since the frequency of intracranial hemorrhage from the BM is high regardless of the number and size of BMs, early treatment such as surgical resection should be considered.

Abbreviations

DTC:differentiated thyroid cancer; RAI:radioactive iodine; BM:brain metastasis; PTC:papillary thyroid carcinoma; FTC:follicular thyroid carcinoma; CT:computed tomography; MRI:magnetic resonance imaging; WBRT:whole brain radiotherapy; SRS:Stereotactic radiosurgery

Declarations

Ethics approval and consent to participate

Protocol of the study was approved by our institutional review board.

Consent for publication

Not applicable.

Availability of data and material

Please contact author if data are needed.

Competing interests

We have no competing interests related to this manuscript.

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Authors' contributions

Noriko Takata conducted this research and wrote this manuscript. Yasushi Hamamoto and Masao Miyagawa provided research advice. Kenji Makita, Hirofumi Ishikawa, Shintaro Tsuruoka and Kei Nagasaki participated data collection and supported the research. Teruhito Mochizuki checked manusucript and provided research advice. All authors read and approved the final manuscript.

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References

1. Carhill AA, Litofsky DR, Ross DS, et al. Long-term outcomes following therapy in differentiated thyroid carcinoma: NTCTCS registry analysis 1987-2012. J Clin Endocrinol Metab. 2015;100:3270-3279.
2. Song H-J, Qiu Z-L, Shen C-T, et al. Pulmonary metastases in differentiated thyroid cancer: efficacy of radioiodine therapy and prognostic factors. Eur J Endocrinol. 2015;173:399-408.
3. Yang J, Liang M, Jia Y, et al. therapeutic response and long-term outcome of differentiated thyroid cancer with pulmonary metastases treated by radioiodine therapy. Oncotarget. 2017;8:92715-92726.
4. Qiu ZL, Song HJ, Xu YH, et al. Efficacy and survival analysis of ^{131}I therapy for bone metastases from differentiated thyroid cancer. J Clin Endocrinol Metab. 2011;96:3078-3086.
5. Chiu AC, Delpassand ES and Sherman SI. Prognosis and treatment of brain metastasis in thyroid carcinoma. J Clin Endocrinol Metab. 1997;82:3637-3642.
6. Slutzky-Shraga I, Gorshtein A, Popovitzer A, et al. Clinical characteristics and disease outcome of patients with non-medullary thyroid cancer and brain metastases. Oncol Lett. 2018;15:672-676.
7. McWilliams RR, Giannini C, Hay ID, et al. Management of brain metastases from thyroid carcinoma: A study of 16 pathologically confirmed cases over 25 years. Cancer. 2003;98:356-362.
8. Jiang X-B, Le C, Zhang G-H, et al. Brain metastases from hepatocellular carcinoma: clinical features and prognostic factors. BMC Cancer. 2012; 12:49:doi: 10.1186/1471-2407-12-49.
9. Ghia AJ, Tward JD, Anker CJ, et al. Radiosurgery for melanoma brain metastasis: the impact of hemorrhage on local control. J Radiosurg SBRT. 2014;3:43-50.
10. Wronski M, Arbit E, Russo P, et al. Surgical resection of brain metastases from renal cell carcinoma in 50 patients. Urology. 1996;47:187-193.
11. Tahmasebi FC, Farmer P, Powell SZ, et al. Brain metastases from papillary thyroid carcinomas. Virchows Arch. 2013;462:473-480.
12. Isoda H, Takahashi M, Arai T, et al. Multiple haemorrhagic brain metastases from papillary thyroid cancer. Neuroradiology. 1997;39:198-202.

13. Tanaka T, Kato N, Aoki K, et al. Cerebellar hemorrhage secondary to cerebellopontine angle metastasis from thyroid papillary carcinoma. Neurol Med Chir. 2013;53:233-236.
14. Tsuda K, Tsurushima H, Takano S, et al. Brain metastasis from papilarry thyroid carcinomas. Mol Clin Oncol. 2013;1:817-819.
15. Choi J, Kim JW, Keum YS, et al. The largest known survival analysis of patients with brain metastasis from thyroid cancer based on prognostic groups. PLoS One. 2016;11:e0154739:doi: 10.1371/journal.pone.0154739
16. Salvati M, Frati A, Rocchi G, et al. Single brain metastasis from thyroid cancer: Report of twelve cases and review of the literature. J Neuro Oncol. 2001;51: 33-40
17. Guelho D, Ribeiro C, Melo Miguel, et al. Long term survival in a patient with brain metastases of papirally thyroid carcinoma. BMJ Case Rep. 2016;doi: 10.1136/bcr-2015-213824.
18. Schlumberger M, Tahara M, Wirth LJ, et al. Lenvatinib versus placebo in radioiodine refractory thyroid cancer. N Engl J Med. 2015;372:621-630.
19. Suyama K, Murakami D, Fujiwara S, et al. Massive arterial bleeding after lenvatinib therapy for thyroid cancer. Int J Cancer Clin Res. 2016; 3:doi: 10.23937/2378-3419/3/6/1074
20. Cabanillas ME, Schlumberger M, Jarzab B et al. A phase 2 trial of lenvatinib (E7080) in advanced, progressive, radioiodine-refractory, differentiated thyroid cancer: A clinical outcomes and biomarker assessment. Cancer. 2015;121:2749-2756

Tables

Due to technical limitations, all tables are only available for download from the Supplementary Files section.

Figures

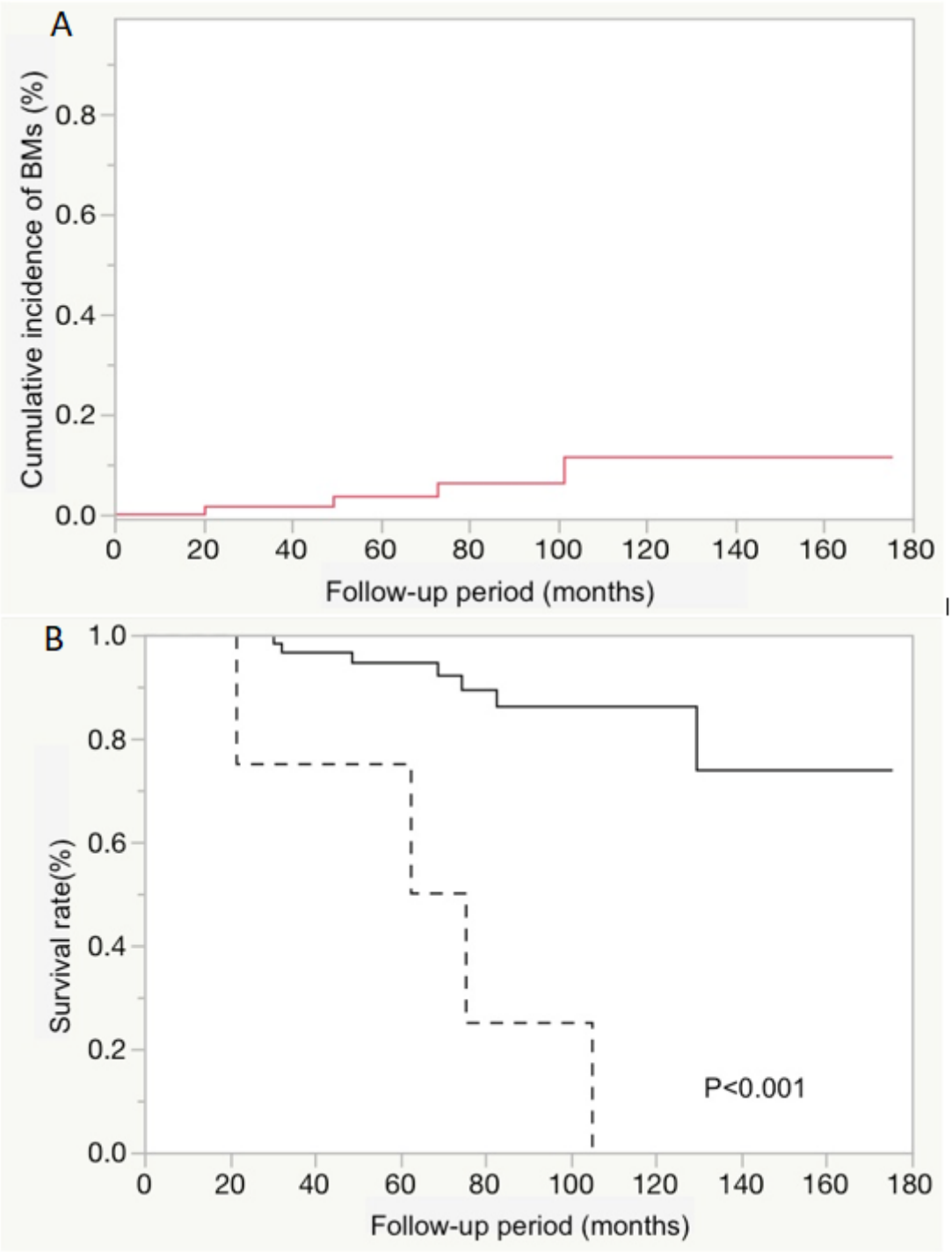

Figure 1

a: Cumulative incidence of brain metastases (BMs). The 5-year incidence of BMs was 3.5% in all patients
b: The survival data by patients with or without brain metastases (BMs). The prognosis of patients with BMs was significantly worse than those without BMs

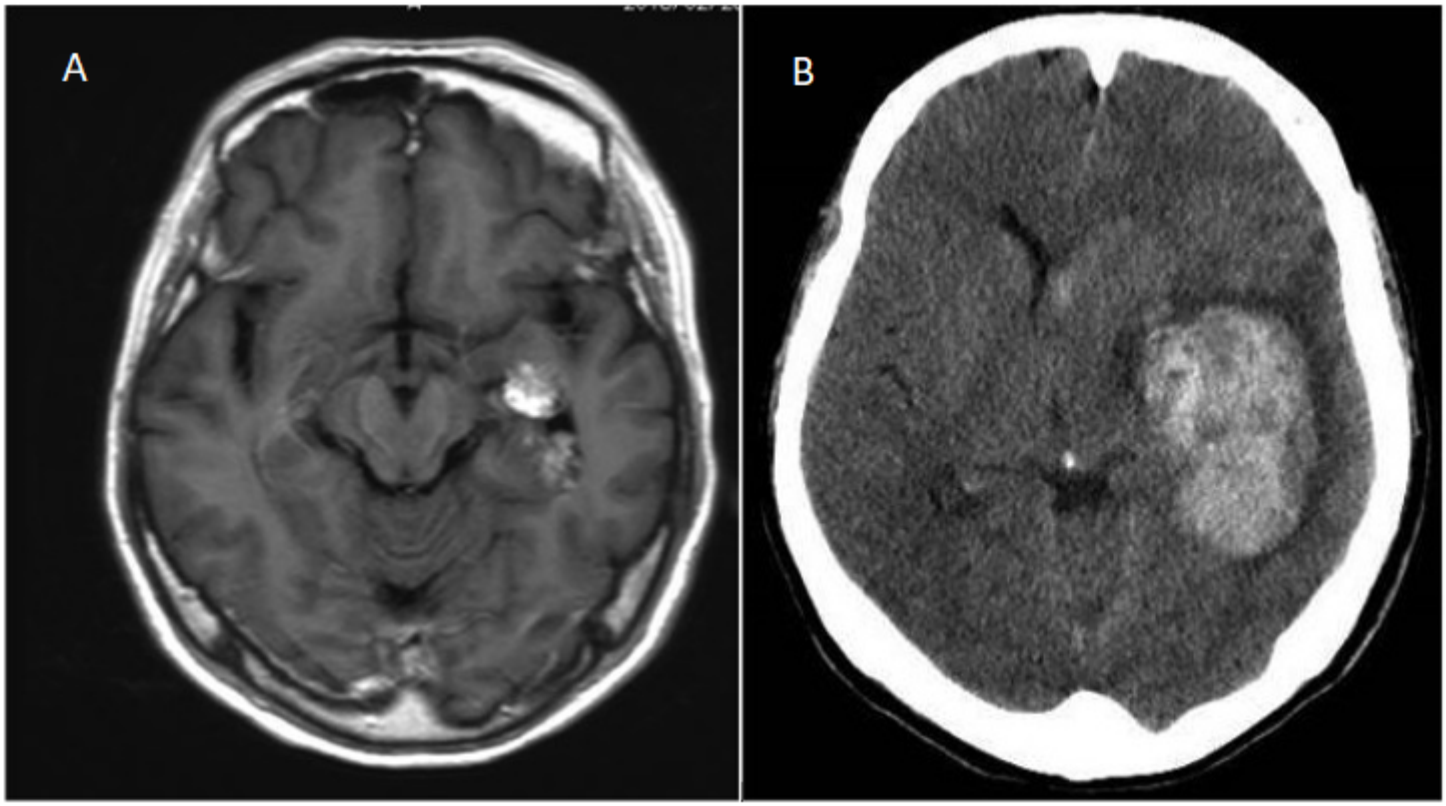

Figure 2

a: T1-weighted axial image with gadolinium enhancement of magnetic resonance imaging (MRI) of the Case 2 on Table 2. Enhanced lesions were detected in right frontal lobe (not shown) and left lateral ventricle b: Computed tomography (CT) after 3.6 months of first MRI. High density hemorrhage was detected, and midline shift was observed

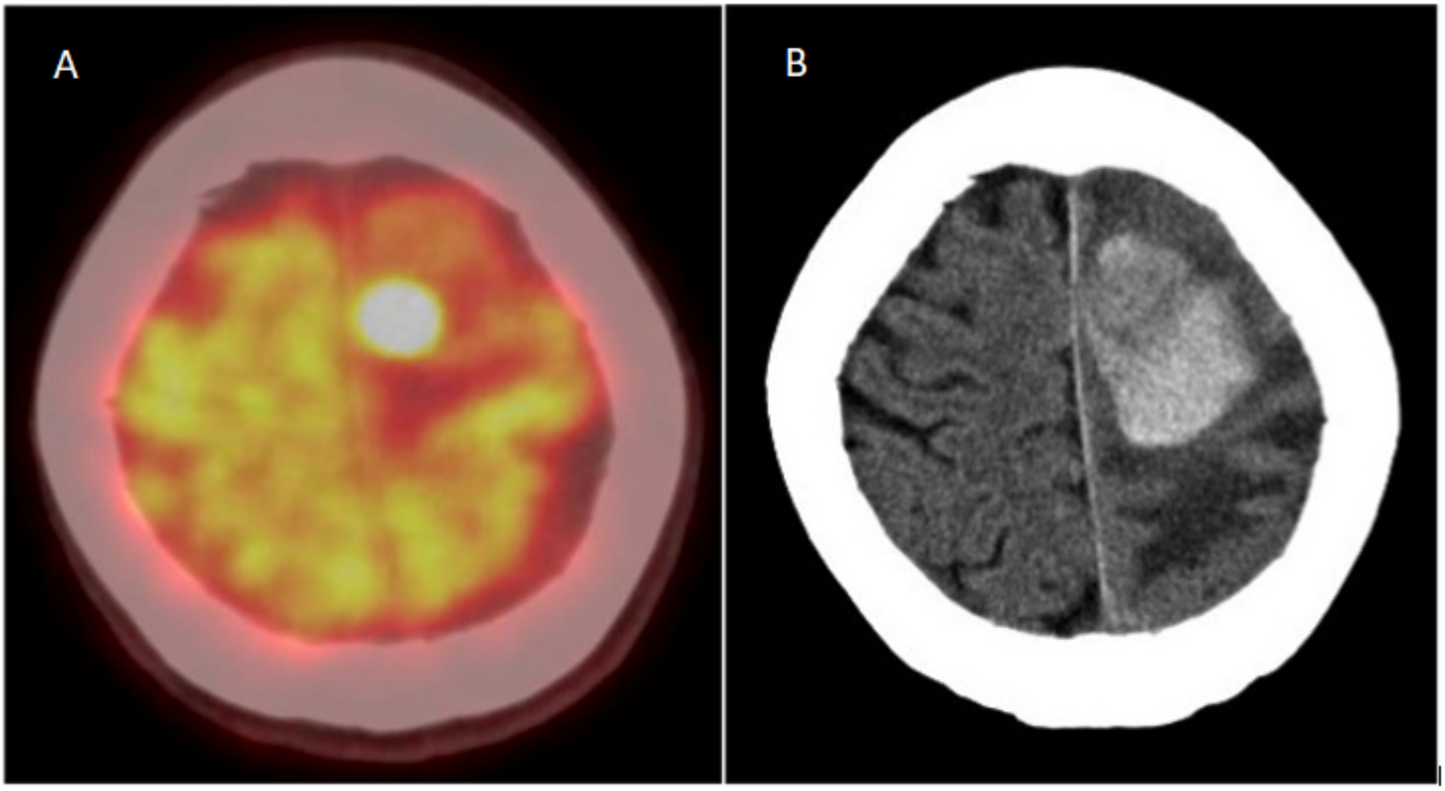

Figure 3

a: Axial fusion image of FDG-PET/CT of the case 3 on Table 2. A 12 mm nodule in diameter was observed in left frontal lobe with brain edema. The lesion shows high FDG uptake (SUVmax=16.19) b: Non-enhanced CT after 1 month of FDG-PET/CT. High density hemorrhage with brain edema was shown in left frontal lobe.

Supplementary Files

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