

Fatal Metastatic Cutaneous Squamous Cell Carcinoma Evolving from a Localized Verrucous Epidermal Nevus

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Key Words

Fatal metastatic cutaneous squamous cell carcinoma · Localized verrucous epidermal nevus · Cutaneous squamous cell carcinoma · Epidermal nevus · Metastasis

Abstract

A malignant transformation is known to occur in many nevi such as a sebaceous nevus or a basal cell nevus, but a verrucous epidermal nevus has only rarely been associated with neoplastic changes. Keratoacanthoma, multifocal papillary apocrine adenoma, multiple malignant eccrine poroma, basal cell carcinoma and cutaneous squamous cell carcinoma (CSCC) have all been reported to develop from a verrucous epidermal nevus. CSCC has also been reported to arise from other nevoid lesions like a nevus comedonicus, porokeratosis, a sebaceous nevus, an oral sponge nevus and an ichthyosiform nevus with CHILD syndrome. Here we report a case of progressive poorly differentiated CSCC arising from a localized verrucous epidermal nevus, which caused both spinal cord and brain metastasis.

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Introduction

Squamous cell carcinoma may occur anywhere on squamous epithelial skin and mucous membranes. Cutaneous squamous cell carcinomas (CSCC) comprise about one fifth of all non-melanoma skin cancers, the incidence rate is steadily increasing in the USA and Europe. CSCC arising from sun-damaged skin have a very low tendency to metastasize. While those

tumours that arise secondary to inflammatory and degenerative processes have a much higher metastasis rate. The mortality rate in patients with metastasis is about 75% [1, 2].

A malignant transformation is known to occur in many nevi such as a sebaceous nevus, a basal cell nevus or a dysplastic nevus, while a verrucous epidermal nevus has only rarely been associated with neoplastic changes. Keratoacanthoma, multifocal papillary apocrine adenoma, multiple malignant eccrine poroma, basal cell carcinoma and CSCC have all been reported to develop from a verrucous epidermal nevus [3–7]. In addition, CSCC have been reported to arise from other nevoid lesions like a nevus comedonicus, porokeratosis, a sebaceous nevus, an oral sponge nevus and an ichthyosiform nevus with CHILD syndrome [8–11]. Here we report a case of CSCC arising from a localized verrucous epidermal nevus.

Case Report

A 50-year-old Asian male presented with a partially pigmented 2-year-old lesion on the upper left side of his back. The lesion measured 3 cm in diameter, was round and had an irregular contour and surface. It had a verrucous pigmented rim on its medial side that measured 6–8 mm, while the prominent exophytic erythematous part measured 2.1 × 2.2 cm (fig. 1). The exophytic part was almost round with an irregular surface. It was friable, bled easily, was tough but not indurated and it was not attached to the underlying structures. The trunk also showed few post-pubertal lentiginos, but no other nevi or seborrheic keratosis. The patient had no other co-morbidities and he was not immune-compromised. He had no personal or family history of skin or any other cancer. The lymph nodes were not enlarged at that time. An immediate total excision biopsy was done. The sutures were removed after 1 week with minimal scarring.

The pathological examination confirmed an epidermal nevus at the periphery of the lesion (fig. 2). The epidermis showed bowenoid features with irregularly sized nuclei, a loss of polarity, dyskeratosis and mitotic figures (fig. 3a, b). Some sections from the periphery of the specimen showed multiple intraepidermal eddies of atypical cells or the Borst-Jadassohn phenomenon (fig. 3c). Sheets of poorly differentiated, atypical, pleomorphic keratinocytes migrated from the epidermis into the whole dermis, hair follicles (fig. 4) and eccrine glands, including a perivascular and perineural invasion (fig. 5a–c). The tumour exhibited a maximal depth of 7 mm (fig. 6).

Atypical cells showed positive staining with cytokeratin markers and other squamous cell carcinoma markers, but they were negative for MART1 and S100. Focal, mild and sparse, subepidermal, lymphocytic infiltrates were found on some sections but were absent in many areas of the lesion. Thorough laboratory and radiological investigations were carried out. The results were: only mildly increased liver enzymes, an elevated C-reactive protein level and a mild impairment in the pulmonary function tests. The diagnosis was CSCC, stage T4N0M0.

The patient was immediately referred to the surgical department for the removal of sentinel lymph nodes. However, the surgeon decided not to excise any lymph nodes as long as the tumour could be totally removed in the absence of enlarged adjacent lymph nodes, demonstrated by clinical and ultrasound examination. The initial bone scan was negative for metastasis.

Six weeks later (8 weeks after his first visit), the patient had a follow-up. Unfortunately, the regional lymph nodes were palpable, while the scar of the primary lesion and the surrounding area remained clear. The swelling was so extensive that it also infiltrated the surrounding subcutaneous tissue, measuring 12 × 17 cm (fig. 7). An excision biopsy was

taken from the lymph nodes and the surrounding subcutaneous tissues confirming the diagnosis of metastatic CSCC. The patient was again operated on for a wide removal of the axillary lymph nodes and adjacent tissues. After this surgical excision, the patient's general condition started to deteriorate. He was transferred to the Al Amal Cancer Hospital for chemotherapeutic and/or radiotherapeutic options; however, he was not eligible for either option and plans for intervention were postponed. The patient's general condition continued to decline with additional refractory anaemia, lymphocytopenia and hypoalbuminaemia.

After another 4 weeks, a bone scan, CT and MRI images showed metastasis in both lungs (fig. 8a) and then 3 weeks later in the spinal cord (fig. 8b) and brain (fig. 9), while the liver was spared. The patient received only palliative care during his entire stay, mainly to treat his anaemia and to control the pain. Eventually, he went into coma and then passed away.

Discussion

The prevalence of verrucous epidermal nevi is about 0.1–0.5% with an equal male-to-female distribution. To the best of our knowledge, only 12 cases of CSCC arising from verrucous epidermal nevi have been reported so far in the literature. Nine cases are displayed in table 1 [7, 12–19], while the data in the remaining 3 cases were inadequate: 2/3 cases were described in poster abstracts [20, 21], and the third case was not available as a full text [22].

Comparing the cases in table 1, CSCC evolving from verrucous epidermal nevi showed an equal sex distribution among males and females. CSCC was more common in Caucasians (4/10 cases) followed by Asians (3/10 cases) and Blacks (2/10 cases). 3/10 were younger than 30 years, and 7/10 were above the age of 40 years (mean age 53.4 years). The 3 younger cases [14, 17, 19] were all females, Caucasian and 2/3 had a good prognosis, including followed-up [14, 19].

In half of the cases, the CSCC was on the trunk (including the present case); in the other half, it was on the limbs: 2 on the right upper limb and 3 on the left lower limb. The adjacent female genitalia were involved in 2/3 cases [18, 19]. The type and distribution of the verrucous epidermal nevi were quite variable: 5/10 nevi were localized, 3/10 nevi were linear and 2/10 nevi were systematized. The head and neck were spared. We also observed that the left upper limbs and the right lower limbs were spared, too. We do not have any explanation for this finding at the present time. It is also remarkable that 4/10 CSCC erupted on the upper trunk and from localized verrucous epidermal nevi [7, 14, 15, and the present case]. Nonetheless, the case of Ichikawa et al. [16] was unique and different, as it developed on the mid-back and from a systematized verrucous epidermal nevus.

Paradoxically, the largest 3 tumours were associated with good prognosis [16, 18, 19], while distant metastasis was associated with relatively small tumours [15, and the present case]. Lymph node metastasis occurred in 4/6 cases. Local metastasis of the tumours into the surrounding subcutaneous tissues occurred in 4/8 cases. In general, the prognosis of CSCC evolving from a localized verrucous epidermal nevus was favourable. 5/6 cases had a good prognosis, with variable lengths of follow-up, ranging from 1 to 5 years (table 1). Distant metastasis, possibly by haematogenous spread, to remote areas happened in 2/8 cases. The reason for distant metastasis in these cases may be inferred to the delay in dissection of sentinel lymph nodes.

Pathological examination revealed well differentiated squamous cell carcinoma in 7/8 studies. Unfortunately, our case was the only one to show poorly differentiated squamous cell carcinoma. In the epidermis, bowenoid changes and the Borst-Jadassohn phenomenon

were encountered in our specimen. They were also present in some biopsies of the other reported cases [12, 15, 21, 22].

Metastasis to the central nervous system remains a major cause of morbidity and mortality in patients with systemic cancers. Brain metastases are the most frequently diagnosed intracranial tumours in adults, with an annual incidence rate estimated at 200,000 cases in the USA alone. This rate is 10 times greater than that for primary brain neoplasm. A variety of systemic malignancies can metastasize to the central nervous system, although the majority of metastases stem from lung cancer (40–50%), followed by breast cancer (20–30%), melanoma (5–10%), lymphoma and various other primary sites, like the gastrointestinal tract (4–6%) and the prostate [23].

Brain metastasis from distant CSCC, and not as a direct extension from head and neck tumours, is extremely rare. Only one case has been reported from a CSCC on the dorsum by an Italian group [24]. The patient was 54 years old and the CSCC developed *de novo*. It was a moderately differentiated squamous cell carcinoma measuring 5 cm in diameter and 8.5 mm in depth. There was no perineural or vascular invasion. The para-aortic lymph nodes were involved, while the lungs and liver were spared. The inguinal lymph nodes were positive and subsequently dissected. Metastasis occurred 11 months after his initial presentation. The authors suggested that the brain metastasis was mainly haematogenous in origin. Ours can be considered the second case of brain metastasis from a distant area and not as a direct extension as in cases of head and neck CSCC.

Spinal cord metastasis has been reported only once from CSCC [25]. The report was on a 73-year-old Asian male, and the excised tumour was located on his right fourth toe. The tumour removal was followed by a lymph node dissection and chemotherapy. Three years later, he developed metastasis in the thoracic region of the spinal cord. There have been no previous reports on metastasis from CSCC from a remote site to the spinal cord. Again the current report can be considered the second case of spinal cord metastasis from a distant CSCC and not as a direct extension of the tumour.

In the present case, apart from the delay in presentation for more than 2 years and the presence of the tumour in a hidden area (on his back), other risk factors contributed to the bad prognosis. Factors for high-risk squamous cell carcinomas have been summarized by Tufaro et al. [26]. A tumour exceeding 2 cm in size, pathologically determined bowenoid features, poor differentiation, perineural invasion and invasion of the surrounding structure are all high-risk factors for tumour spread. An invasion depth of >4 mm or a Clark level IV has been associated with a 5-fold increase in metastatic risk [26].

There is no consensus on elective sentinel biopsy or lymph node dissection in CSCC which does not involve the head and neck regions, especially if there are no clinical or radiological signs of node involvement. In most studies on high-risk CSCC, intervention for N0 remains unidentified, with unproven benefit. Moreover, the usefulness of lymph node dissection is arguable, as 52% of the patients who underwent lymph node dissection for nodal involvement had disease recurrence and 75% of these patients developed distant metastasis [27].

In conclusion, CSCC evolving from a localized verrucous epidermal nevus is rare, but it might be underreported. Careful uniform pathological reporting is also crucial for identifying high-risk tumours. The depths of the lesions, perineural and perivascular infiltration are factors that favour metastasis. Two recently published studies [7, 19] showed a good prognosis after the excision of sentinel lymph nodes, which may be an advice for clinicians to excise suspected sentinel lymph nodes immediately. Delayed excision of sentinel lymph nodes may carry a bad prognosis as in our case and the case described by Levin et al. [15].

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Table 1. The data of published studies on CSCC arising from verrucous epidermal nevi, including the present case

	Age, years/ sex	Country/ ethnicity	Site/ tumour size	Type of epidermal nevus	Thickness/ differentiation	Lymph node involvement	Metastasis	Prognosis/ follow-up
Swint and Klaus, 1970, [12]	64 / male	USA/ Caucasian	left thigh/ 7 cm	linear, left lower limb	N/A/ well differentiated	N/A	N/A	N/A
Dogliotti and Frenkel, 1978, [13]	41 / male	South Africa/ Black	right hand and forearm/ several cm	linear, right upper limb	N/A/ well differentiated	N/A	tumour reached bone level	N/A
Cramer et al., 1981, [14]	17 / female	USA/ Caucasian	right breast/ 1×1.2 cm	localized	N/A/ well differentiated	N/A	N/A	good/ 1 year
Levin et al., 1984, [15]	69 / male	USA/ N/A	chest, right upper side/ 2 cm	localized	N/A/ well differentiated	positive after 8 months	lungs	N/A
Ichikawa et al., 1996, [16]	74 / male	Japan/ Asian	mid-back/ 13×15 cm	systematized	N/A	no	no distant metastasis	good/ 1 year
Affleck et al., 2005, [17]	28 / female	UK/ Caucasian	right arm/ 0.5 and 0.3 cm	localized	2.6 and 1.5 mm/ well differentiated	N/A	local recurrence of first tumour	N/A
Masood and Narayan, 2009, [18]	81 / female	USA/ African-American	left thigh and left labium/ 25×40 cm	linear, left thigh	N/A/ well differentiated	no	no distant metastasis	good/ 2 years
Turk et al., 2012, [19]	28 / female	Turkey/ Caucasian	left groin and labia/ 10×20 cm	systematized, left side of the body	N/A	positive	no distant metastasis	good/ 5 years
Toya et al., 2012, [7]	82 / female	Japan/ Asian	upper back near left axilla/ 2.5 cm	localized	N/A/ well differentiated	positive	subcutaneous tissue	good/ 1 year
Present case, 2013	50 / male	Qatar/ Asian	upper back near right axilla/ 2.1×2.3 cm	localized	7 mm/ poorly differentiated	positive after 2 months	subcutaneous tissue, lungs, spine and brain	bad/ passed away within 8 months



Fig. 1. A partially pigmented 2-year-old lesion on the upper left side of our patient's back. The lesion measured 3 cm in diameter, was round and had an irregular contour and surface. It had a verrucous pigmented rim on its medial side that measured 6–8 mm, while the prominent exophytic erythematous part measured 2.1 × 2.2 cm.

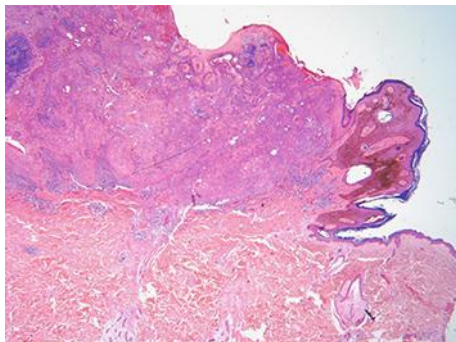


Fig. 2. The pathological examination confirmed an epidermal nevus at the periphery of the lesion. H&E staining, ×50 magnification.

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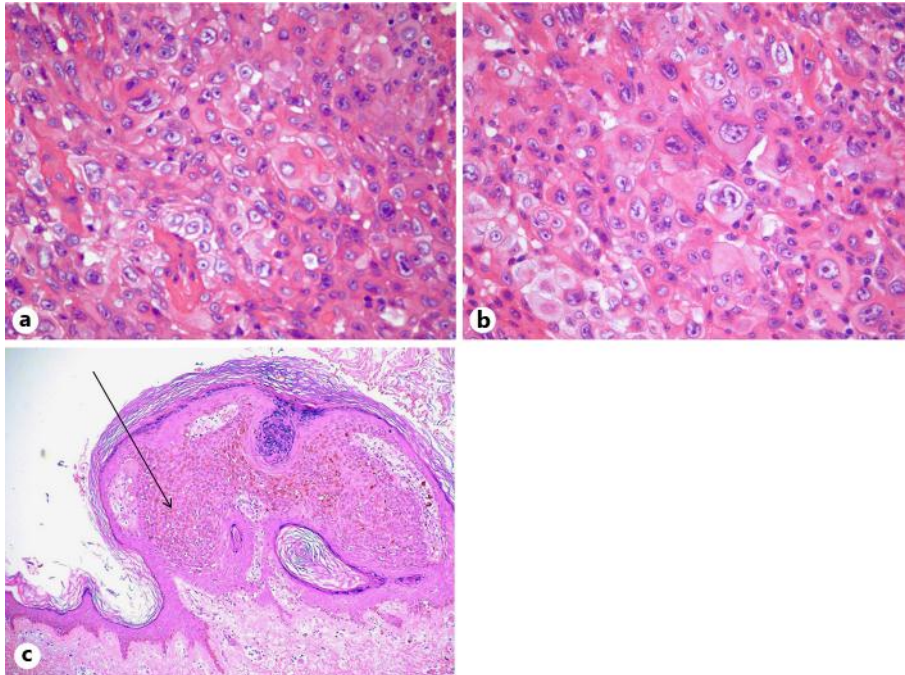


Fig. 3. **a, b** The epidermis showed bowenoid features with irregularly sized nuclei, a loss of polarity, dyskeratosis and mitotic figures. **c** Some sections from the periphery of the specimen showed multiple intraepidermal eddies of atypical cells or the Borst-Jadassohn phenomenon (arrow).

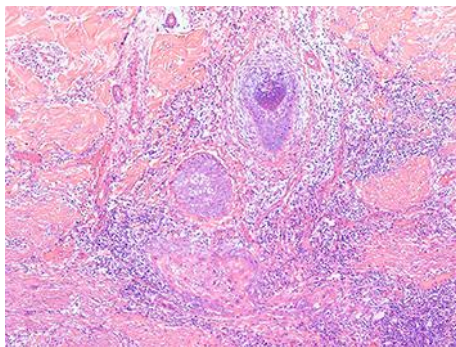


Fig. 4. Sheets of poorly differentiated, atypical, pleomorphic keratinocytes migrated from the epidermis into hair follicles.

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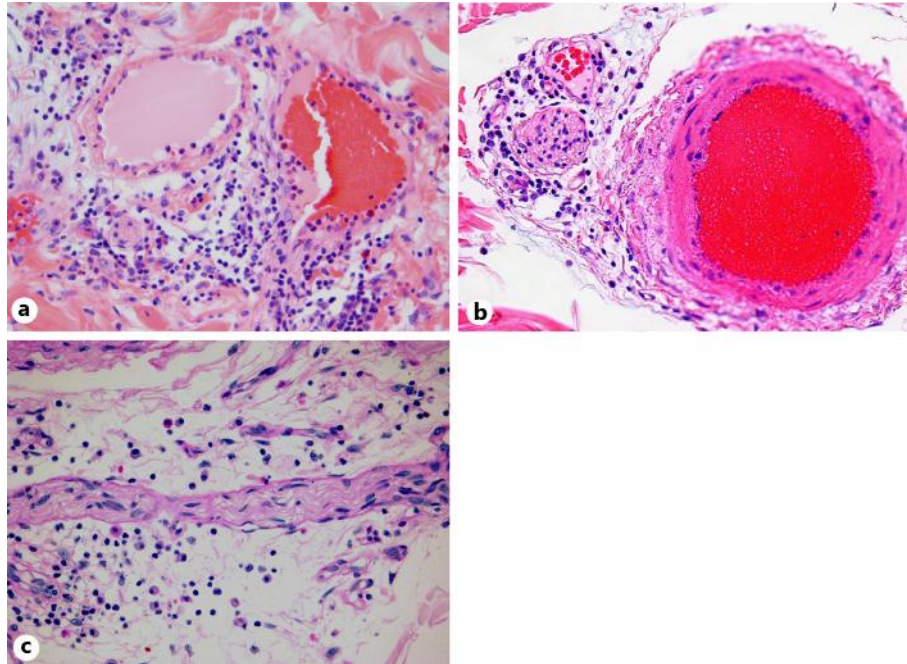


Fig. 5. Pathological examination proved a perivascular and perineural invasion.

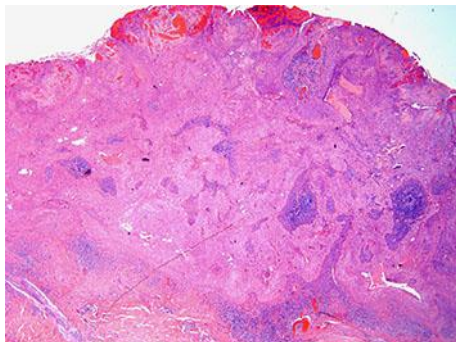


Fig. 6. The tumour exhibited a maximal depth of 7 mm.

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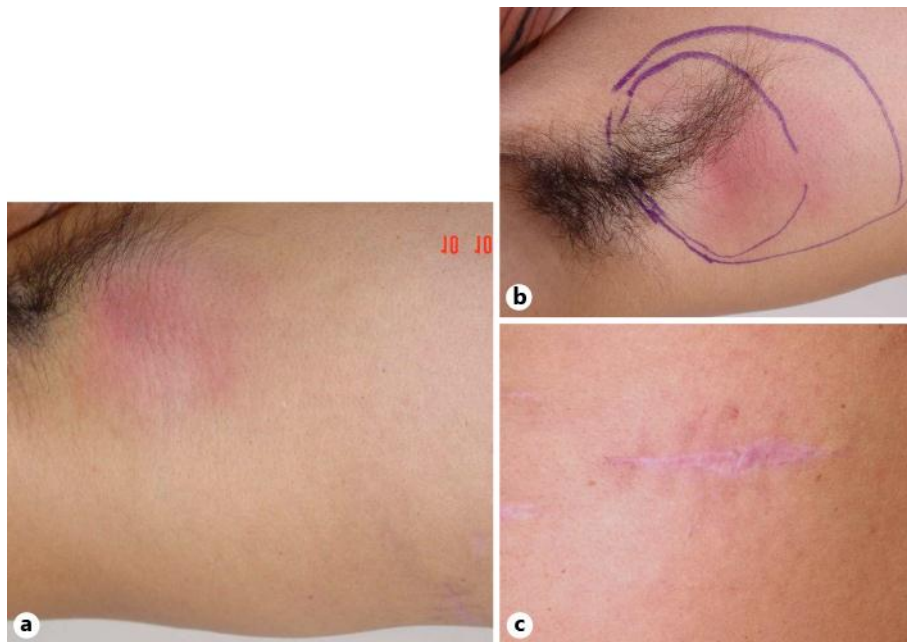


Fig. 7. After 6 weeks, the regional lymph nodes were palpable. The swelling was so extensive that it also infiltrated the surrounding subcutaneous tissue measuring 12 × 17 cm.

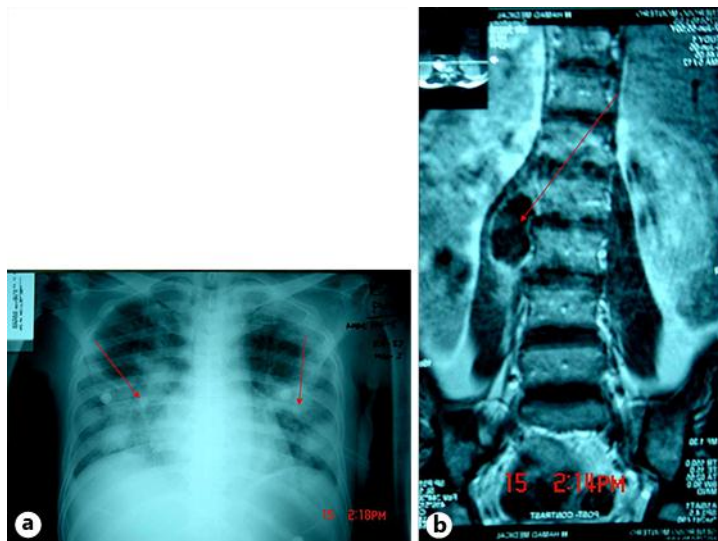


Fig. 8. Metastasis is visible in both lungs (a) and in the spinal cord (b) on a CT image and bone scan, respectively.

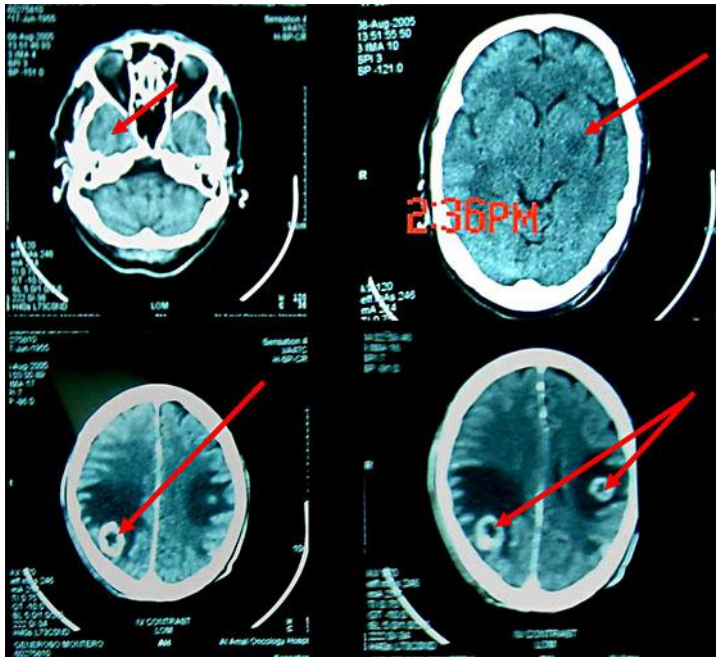


Fig. 9. Metastasis is visible in the brain on MRI images.