Metastasis of Sarcomatoid Malignant Mesothelioma With *p16/CDKN2A* Deletion Presented as a Subcutaneous Mass in the Back: a Case Report and Review of Literature

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Case Report

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Abstract

Background: Sarcomatoid malignant mesothelioma (MM) is a rare and aggressive disease, and its diagnosis is challenging.

Case presentation: A 60-year-old man was found a recurrent mass in his right back after the initial resection. A chest CT found right pleural thickening, nodular pleural thickening, pleural effusion, mediastinal and right infraclavicular lymph nodes enlargement, which indicated a right pleura MM. Immunohistochemical (IHC) stains of the resected mass showed sarcomatous atypical spindle cells, which were positive for CK 1/3, CK 5/6, WT1, podoplanin and vimentin, and negative for Napsin A, TTF-1 and CDX2, and fluorescent in situ hybridization (FISH) detected homozygous *p16/CDKN2A* deletion. The association of the chest CT features and the mass assessment confirmed metastatic MM in the subcutaneous layer of the back. Moreover, PET-CT showed multiple metastases in his brain. He developed massive right pleural effusion and chest tightness soon, and the mass kept growing despite of the local and systemic treatments, and he died from pulmonary failure in 3 months.

Conclusion: We described an extremely rare subcutaneous metastasis in the back from sarcomatoid MM. And we made the diagnosis by both histological and molecular analysis of the metastatic lesion. MM patients most likely have subcutaneous metastasis on head, they usually develop pleural effusion, chest pain or dyspnea, and their prognosis is very poor because of late diagnosis and insensitivity to current therapies.

Background

Malignant mesothelioma (MM) is a rare malignancy which arises from mesothelial or subthelial layer of the pleura (80–90%), peritoneum (10–15%), pericardium and tunica vaginalis testis(< 5%)[1]. It has been increasing over the past decade, and most cases are associated with exposure to asbestos. It is divided into three subtypes: epithelioid type, sarcomatoid type and biphasic type[2], and sarcomatoid MM is the most aggressive type. It is usually difficult to differentiate from benign mesothelial pleural proliferations or other cancers[3]. Because of its nonspecific symptom, MM is often diagnosed at late stage with distal metastases including lymph nodes, lung, liver, adrenal glands and kidney[4]. However, it is very rare to see a metastatic lesion within cutaneous or subcutaneous tissue, which is most likely via hematogenous spread. To our knowledge, only 3 such cases of sarcomatoid MM were previously reported[4–6].

Case Presentation

A 60-year-old man was referred to the General Surgery Department for a growing subcutaneous mass in the right back. He felt slight pain and discomfort when lying down. There was no local swelling or pruritus around the mass. An ultrasound showed a large tumor with hemorrhage (Diameter: 13.8*4.7 cm) in the muscularis. He was generally healthy and had no mental or inherited disease. He was admitted and received radical tumor resection under general anesthesia. Unexpectedly, the mass recurred quickly two

weeks after surgery. A MRI showed tumor recurrence which intruded into thoracic cavity (Fig. 1). While, a chest CT found right pleural thickening, nodular pleural thickening, pleural effusion, mediastinal and right infraclavicular lymph nodes enlargement (Fig. 2A and 2B). And a needle biopsy of the right pulmonary nodule was performed, which reported few atypical cells.

The histological features of the resected mass revealed that sarcomatous atypical spindle cells with enlarged and elongated nuclei were arranged in fascicles. Immunohistochemical (IHC) stains were positive for cytokeratin (CK) 1/3, CK 5/6, WT1, podoplanin and vimentin, with focal positivity of CAM 5.2, and negative for carcinoma markers, including Napsin A, thyroid transcription factor 1 (TTF)-1 and caudal-related homeobox gene 2 (CDX2) (Fig. 3). Calretinin was not found expressed in this case. Myogenic marker desmin was also negatively expressed. Ki-67 index was 80% (Fig. 3). Fluorescent in situ hybridization (FISH) in cytology specimens showed homozygous *p16/CDKN2A* deletion (Fig. 4). Combined with clinical data, the histopathological diagnosis supported sarcomatoid MM with subcutaneous metastasis.

By a multi-disciplinary team (MDT) discussion, high-intensity focused ultrasound (HIFU) was used to treat the local recurrence. Meanwhile, one course of albumin paclitaxel (300 mg d1) and cisplatin (35 mg d1-3) was intravenously administrated. 2 week later, a PET-CT found that there was necrosis in the center of the subcutaneous mass, the right pulmonary nodule was as before, the mediastinal and right infraclavicular lymph nodes were smaller, but multiple metastases were seen in the brain (Fig. 5).

Afterwards, radiation was also performed on the mass. But the patient felt aggravating chest tightness and mild pain on the back during this period. Another chest CT found massive right pleural effusion. So pleural aspiration drainage was done to relieve the symptom, approximately 2000 ml of hemorrhagic pleural effusion was drained from the chest cavity. The tumor markers of the pleural effusion were elavated: CA-123 1456.1 U/ml, CA-211 6.8 ng/ml. Twice PD-1 inhibitor (Camrelizumab) (200 mg) was administrated, and three times intrapleural chemotherapy of cisplatin (40 mg) was done. 1 month later, a chest CT showed that right pulmonary nodule was stable, the mediastinal and right infraclavicular lymph nodes decreased, but the tumor in the back still significantly increased (Figure Fig. 2D and 2D). The patient discharged during the chemotherapy interval. However, he got worse soon and ultimately succumbed to pulmonary failure in 1 month after discharge.

Discussion

MM a rare malignant disease, and its diagnosis is usually challenging for pathologists[7]. Because its phenotype varies among patients, and it mimics benign reactive mesothelial proliferations and other cancers. In many cases, only cytological material or a limited amount of tissue is available for pathologic evaluation [8]. Sometimes, video-assisted thoracoscopic surgery (VATS) is necessary for a deep and large biopsy and assessment of its respectability[9, 10]. The International Mesothelioma Interest Group recommends that at least 2 mesothelial (calretinin, CK 5 or 5/6, WT1 and podoplanin) and 2 carcinoma markers (Claudin 4, MOC31, CEA, BER-EP4, BG8, TTF-1 and Napsin A) for IHC differential diagnosis[11].

Recent studies showed that *BAP1* mutations and *p16* deletions by FISH were reliable in differentiating malignant mesotheliomas from benign reactive mesothelial proliferations[7, 12]. Several studies have reported *p16/CDKN2A* deletions in up to 80% of primary MM, depending on the histologic subtype (90–100% of sarcomatoid type; 70% of epithelioid and biphasic types)[13]. A study reported that P16 immunoreactivity in stromal cells of MM had significant relation with the patients' high exposure to asbestos[14]. And the presence of a *p16* homozygous deletion correlates with shorter survival in patients with MM[15]. Recently, circulating miRNAs and extracellular vesicles (EVs) are discovered to be novel and non-invasive biomarkers for early detection, differential diagnosis and predicting prognosis of MM[16, 17]. The resected tumor specimen of this case was positive for CK5/6, WT1 and podoplanin, and negative for Naspin A and TTF-1, which meets the criteria above. Also, the pathological features of sarcomatous atypical spindle cells of this case indicated sarcomatous type of MM. Further FISH detected homozygous *p16/CDKN2A* deletion. This result demonstrates that a metastatic mass is also a reliable diagnostic tissue in the intractable MM case, which has not been verified in the previous studies.

CT features of MM include unilateral pleural effusion, nodular pleural thickening, interlobar fissure thickening, calcified pleural plaques, chest wall involvement and hilar and mediastinal lymph nodes enlargement[18]. However, its sensitivity and specificity are only 70%[19]. MRI can provide additional information of invasive growth of MM such as invasion of the diaphragm, endothoracic fascia and chest wall[20]. PET-CT can identify MM from benign disease, but not metastatic pleural malignancy[21]. And PET-CT is able to indentify nodal and extrathoracic metastases. A study found that Mean SUVmax value was higher in sarcomatoid (11.8 ± 4.6) and biphasic type (9.3 ± 7.0) rather than in epithelioid type (6.9 ± 3.8) ($P < 0.01$), and high SUVmax values were significantly associated with a worse prognosis[22]. We found brain metastases by PET-CT, and the SUVmax of the right lung nodule in this case was as high as 19.0, which indicated highly malignancy.

It is common to see lymph nodes and organ involvement. As we noticed, there were lymph nodes, subcutaneous and brain metastases in this case. The disseminating routes of MM are direct invasion, lymphatic and hematogenous spread[23]. The solitary mass in the back was probably via hematogenous in this case. To our knowledge, there are 18 case reports of cutaneous or subcutaneous metastases from MM [4–6, 23–36] (Fig. 6), but only 3 sarcomatoid type of MM among them[4–6]. The data of the previous researches indicated that the most common cutaneous or subcutaneous metastases from MM occurred on head, chest pain or dyspnea was a main symptom, about half of the patients suffered pleural effusion, they usually received chemotherapy, and 1-year-survival rate was only 20% (Fig. 6).

The majority of patients with MM develop breathlessness with pleural effusion[37]. Therapeutic pleural aspiration and chemical pleurodesis are two ways to control pleural fluid and improve patients' quality of life[37]. Pleural aspiration and intrapleural chemotherapy of cisplatin was done in this case, but its effectiveness of intrapleural cisplatin was uncertain since the follow-up was too short.

Generally, MM is incurable disease, the median survival period is less than 1 year[38], and the 5-year-survival rate is only 5%[39]. A sarcomatoid type is associated with a worst outcome, with a median

survival of just 4 months[37]. This case was found multiple distant metastases and deteriorated very quickly, and the patient died within 3 months since initial diagnosis. Surgery is limited only for MM patients in early stage. Based on our experience, local resection of a subcutaneous metastatic lesion was not a good option, since it turned out a quick recurrence. A needle biopsy might be worthy doing for diagnosis. HIFU therapy rather than radiation showed a therapeutic potential. Systemic treatment of chemotherapy and immunotherapy are delivered on the patient, but MM is highly resistant to them specially the metastastic lesion. A small number of studies showed that pemetrexed/raltitrexed plus cisplatin/carboplatin could achieve better response rates[40, 41]. PD-L1 expression is relatively common (> 30%) for MM samples[42], and it is related to poor prognosis in MM patients[43]. Immunotherapy such as nivolumab is being on clinical trials as a second or third line treatment for MM[2, 44]. In this case, the mediastinal and right infraclavicular lymph nodes seemed sensitive to cytotoxic agents, however, the pulmonary nodule and the subcutaneous mass were both resistant to the agents. Hence, more clinical trials focusing on effective agents should be conducted in the future.

Conclusion

In conclusion, we presented an extremely rare case of a subcutaneous metastatic mass from right pleural sarcomatoid MM. We made the diagnosis by both histological and molecular analysis of the subcutaneous lesion instead of a limited amount of lung tissue biopsy. PET-CT was useful to indentify extrathoracic metastases. Besides, MM patients most likely have subcutaneous metastasis on head, they usually develop pleural effusion, chest pain or dyspnea, and their prognosis is very poor because of late diagnosis and insensitivity to chemotherapy or other treatments.

Abbreviations

MM: malignant mesothelioma; FISH: fluorescent in situ hybridization; MDT: multi-disciplinary team; HIFU: high-intensity focused ultrasound; IHC: Immunohistochemical; CK: cytokeratin; TTF-1: thyroid transcription factor 1; CDX2: caudal-related homeobox gene 2; VATS: video-assisted thoracoscopic surgery; EVs: extracellular vesicles.

Declarations

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Authors' contributions

KBC, YJH performed histological evaluation, made the pathological diagnosis and drafted the manuscript. YJH performed the immunohistochemistry. GPX performed the FISH examination. LinC provided PET-CT images. KBC, XLJ, HZ edited the images and tables. YH, ZWW, LC advised on

manuscript preparation and made revision to the final manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The dataset supporting the conclusion of this article is included within the article.

Ethics approval and consent to participate

This work has been approved by Medical Ethics Committees of the Second Affiliated Hospital of Zhejiang University, School of Medicine (approval number is 2020-514), and informed consent form has been obtained from a relative of the patient.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures

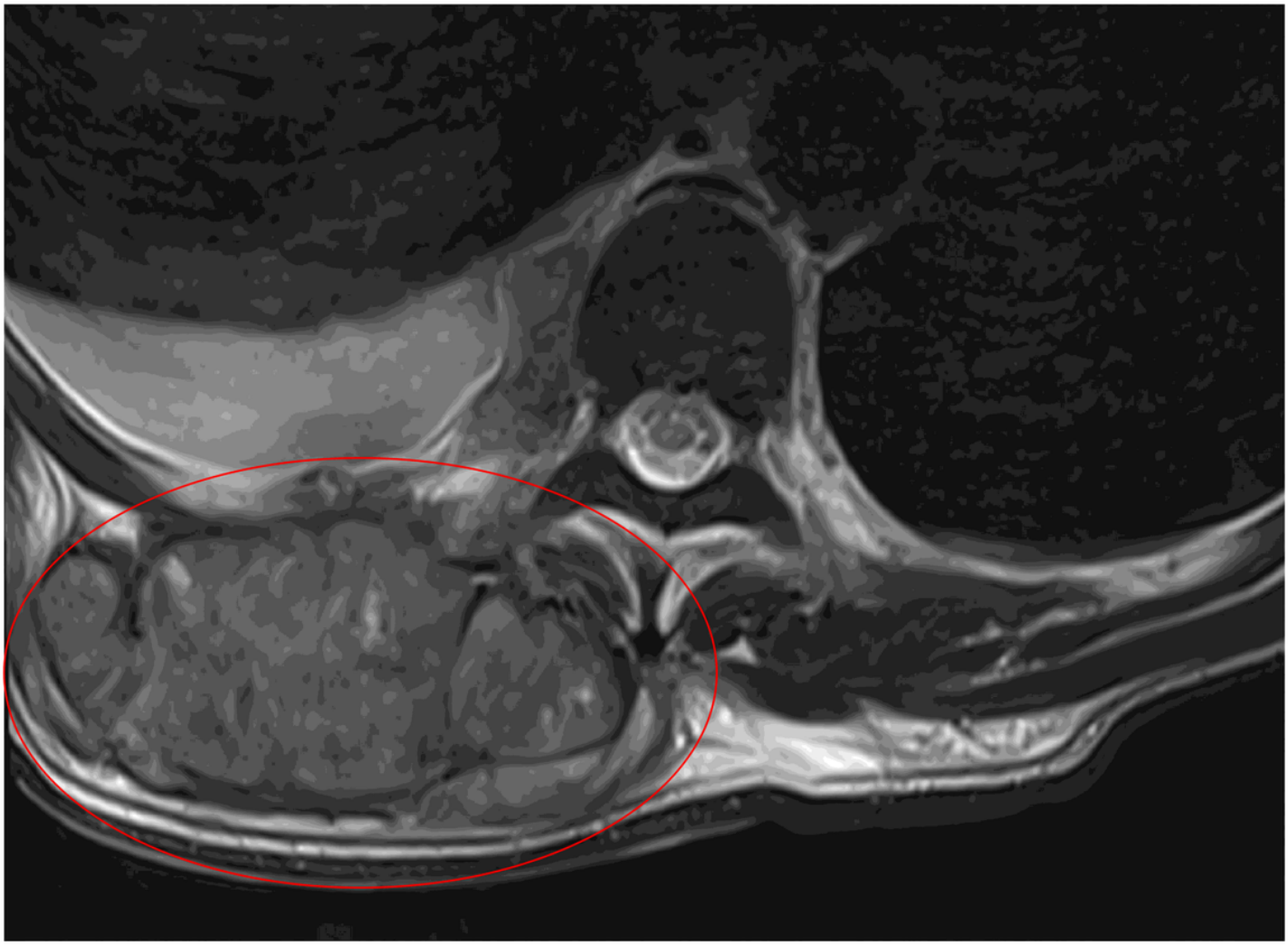
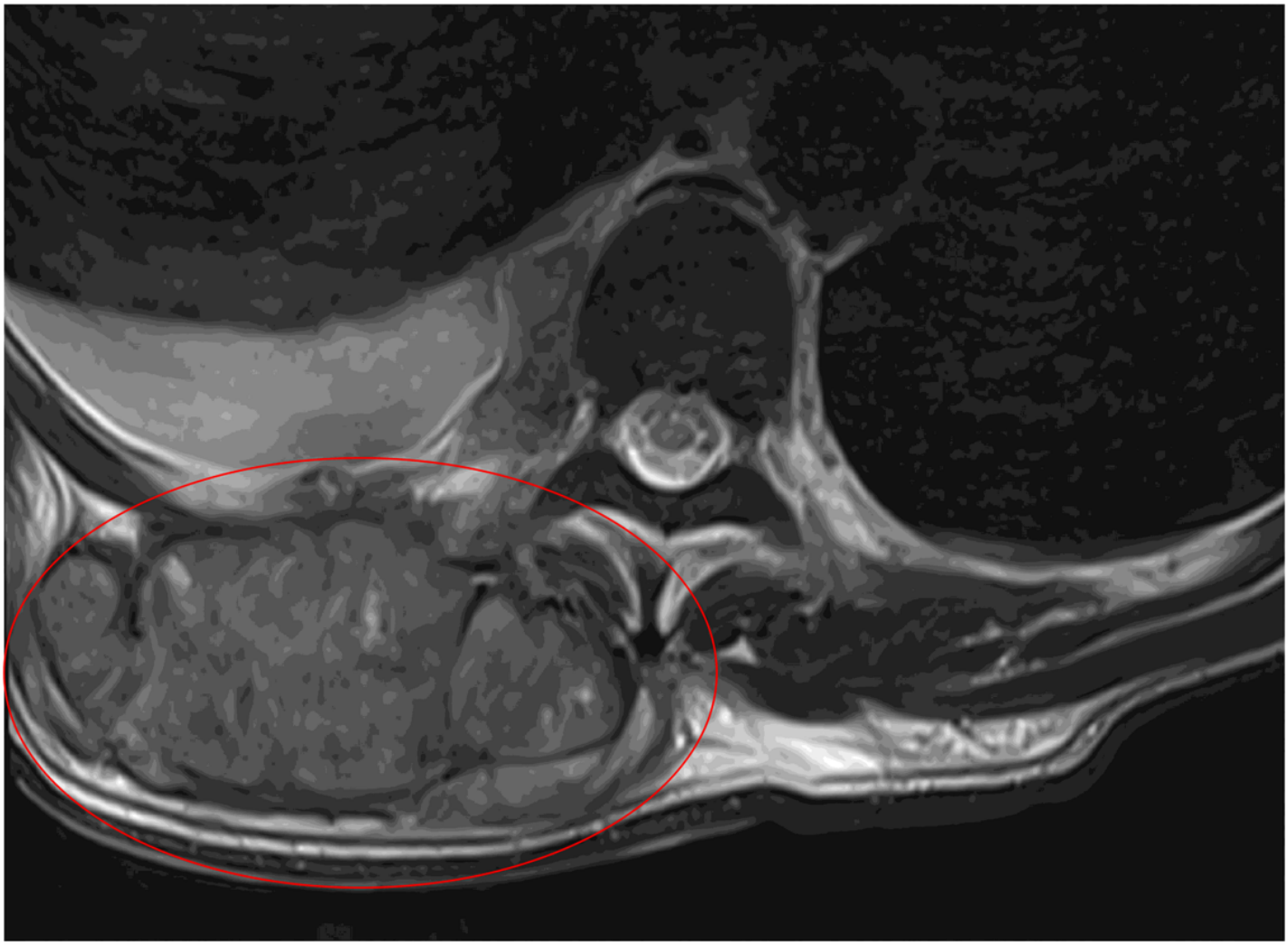


Figure 1

MRI showed an irregular tumor in the back which intruded into the thoracic cavity.



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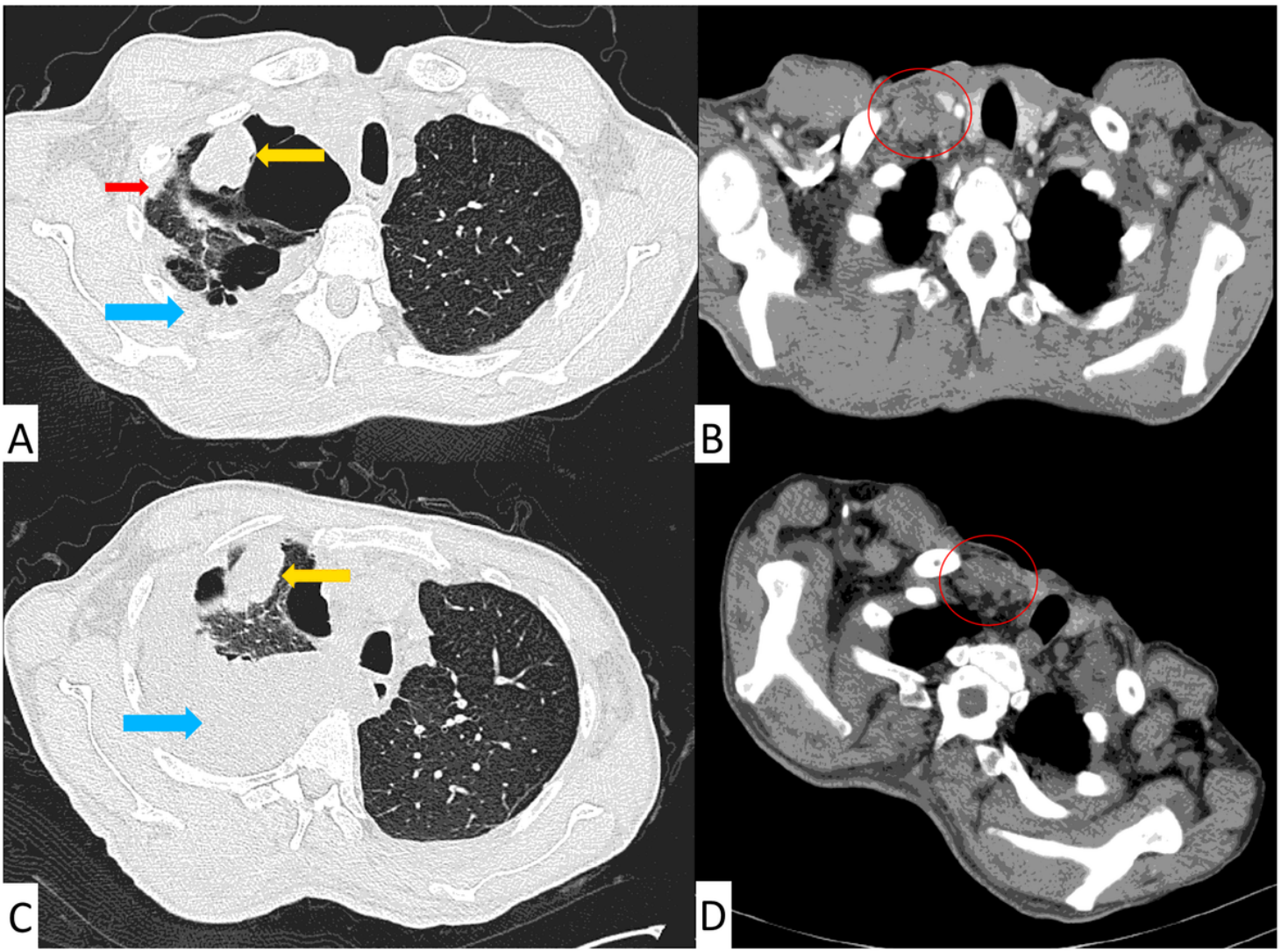
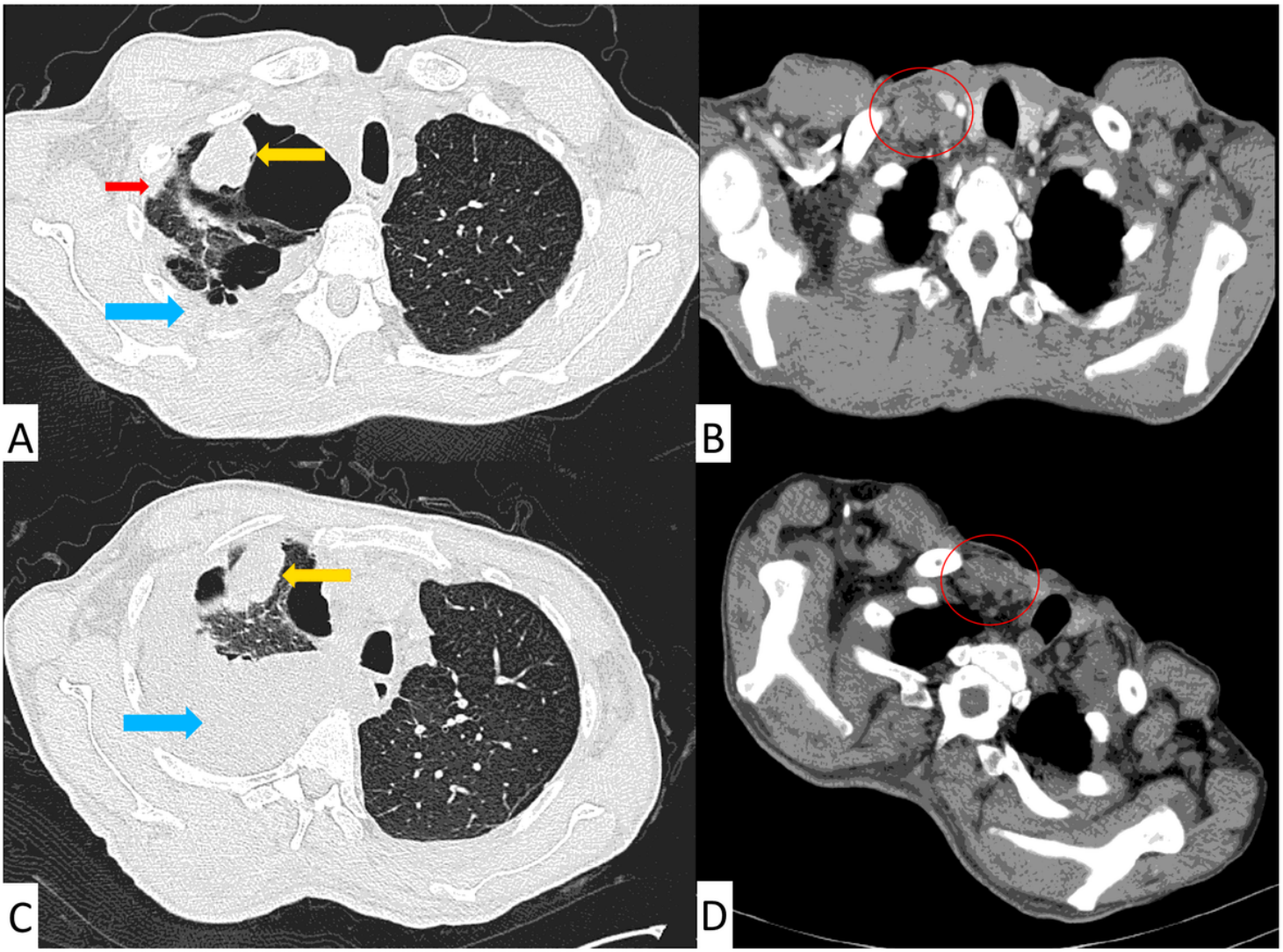


Figure 2

A. CT showed right pleural thickening (red arrow), nodular pleural thickening (yellow arrow) and mild pleural effusion (blue arrow). B. right infraclavicular lymph nodes enlargement. C. the nodular pleural thickening (yellow arrow) was stable and the pleural effusion (blue arrow) increased after treatment. D. the right infraclavicular lymph nodes decreased after treatment.



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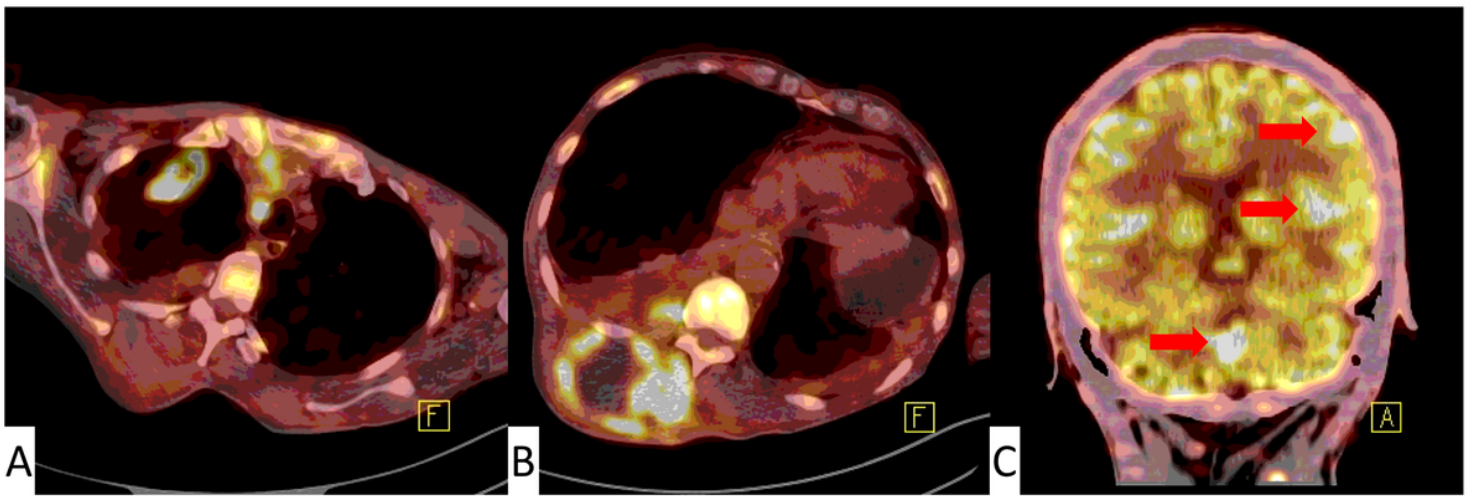
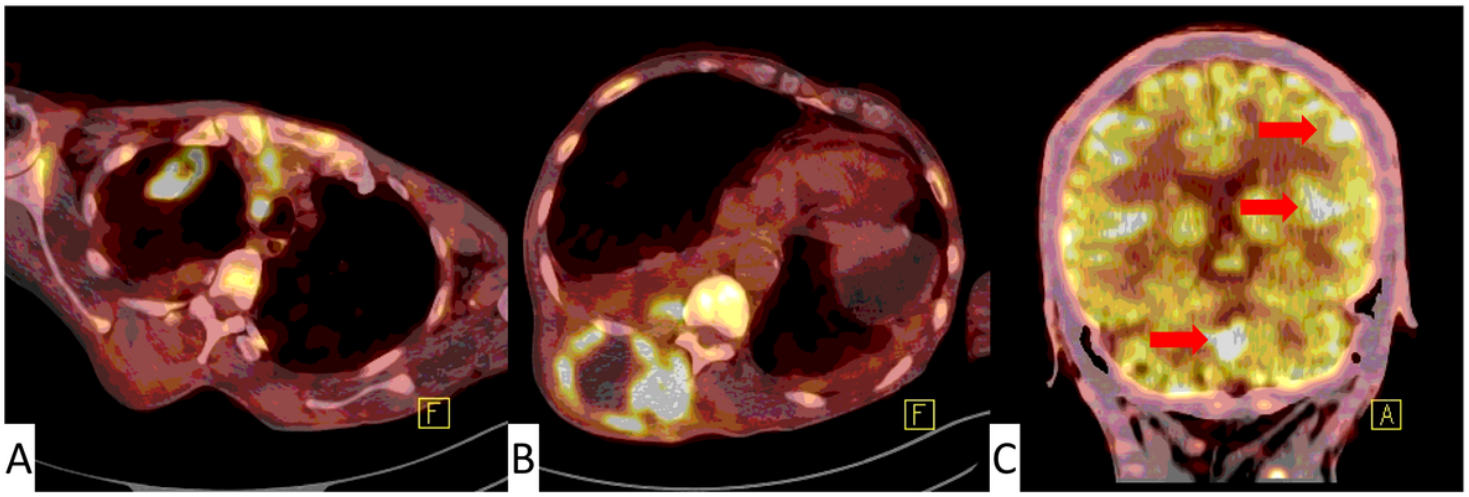


Figure 3

Microscopic features of the subcutaneous mass in this case (Magnification ×200). A. Hematoxylin-eosin staining of tumor specimen showed sarcomatous atypical spindle cells with enlarged and elongated nuclei were arranged in fascicles. B. CK(cytokeratin)1/3 positive. C. CK5/6 positive D. Wilm's tumor 1 (WT)-1 postive E. Podoplanin postive F. Vimentin positive G. Napsin A negative H. Thyroid transcription factor 1 (TTF)-1 negative I. Ki-67 index was 80%.



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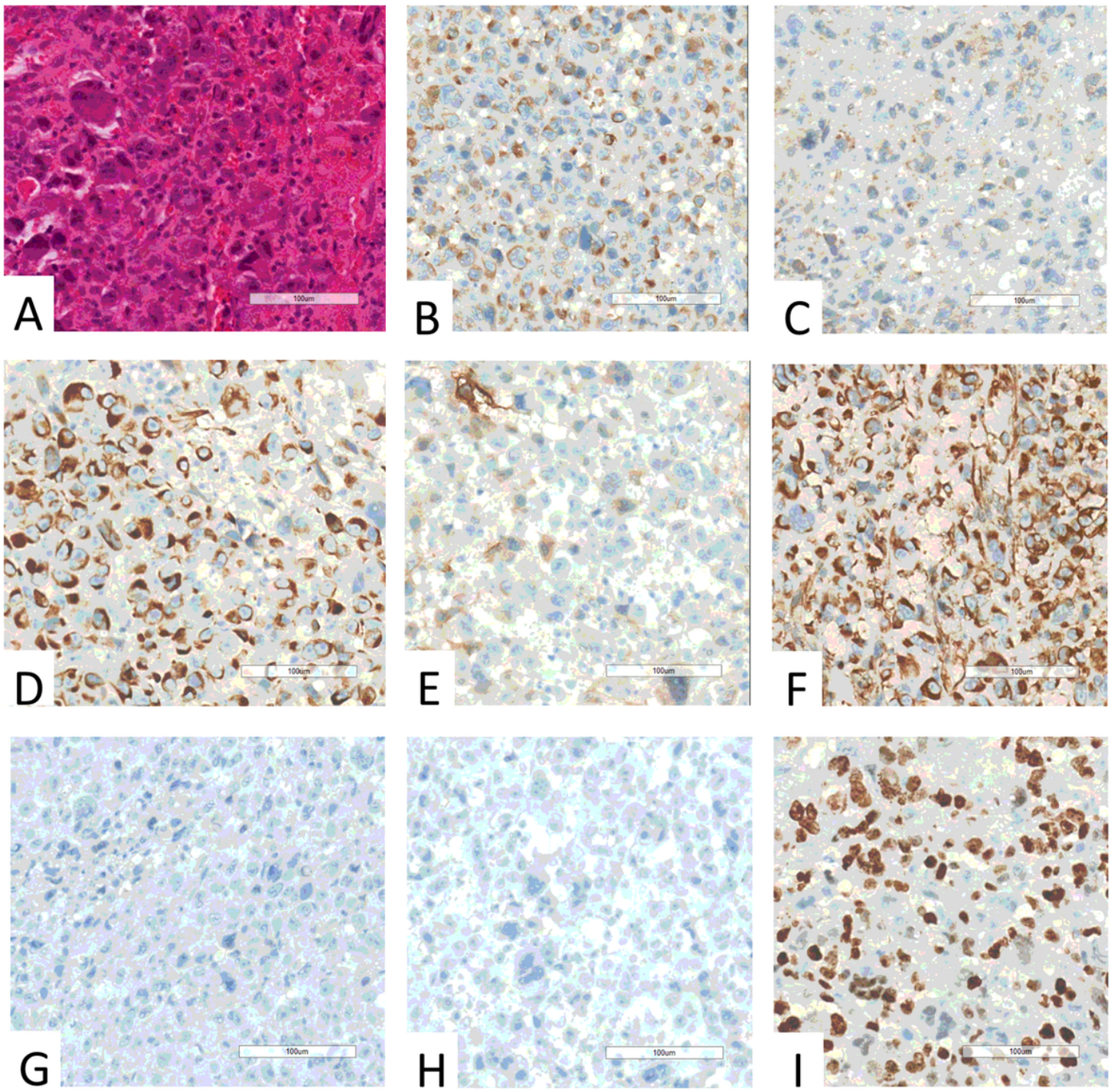
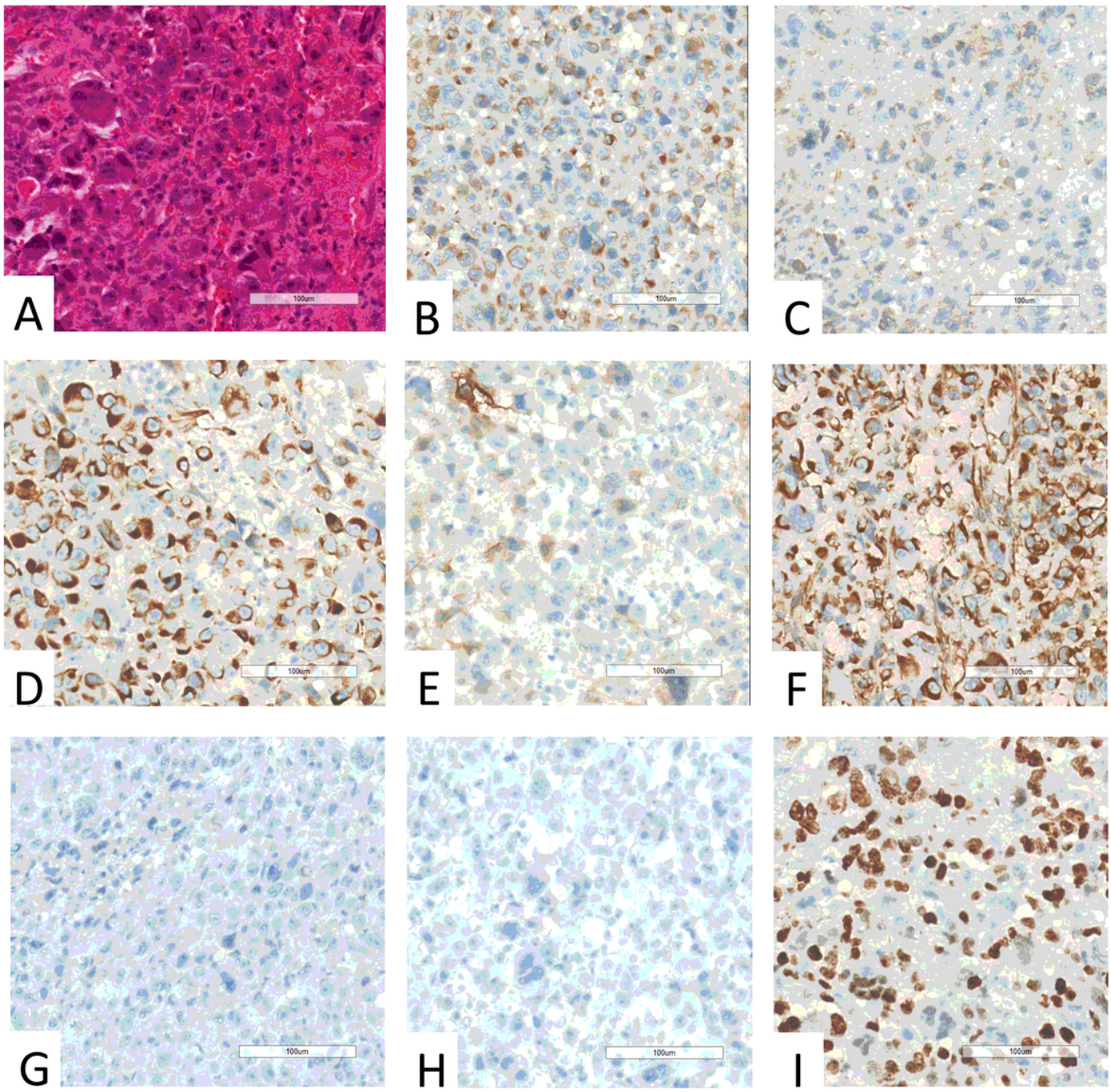


Figure 4

Fluorescent in situ hybridization (FISH) in cytology specimens showed p16 deletion (magnification ×1000): only 2 green signals (9p centromere) and no red signal (p16).



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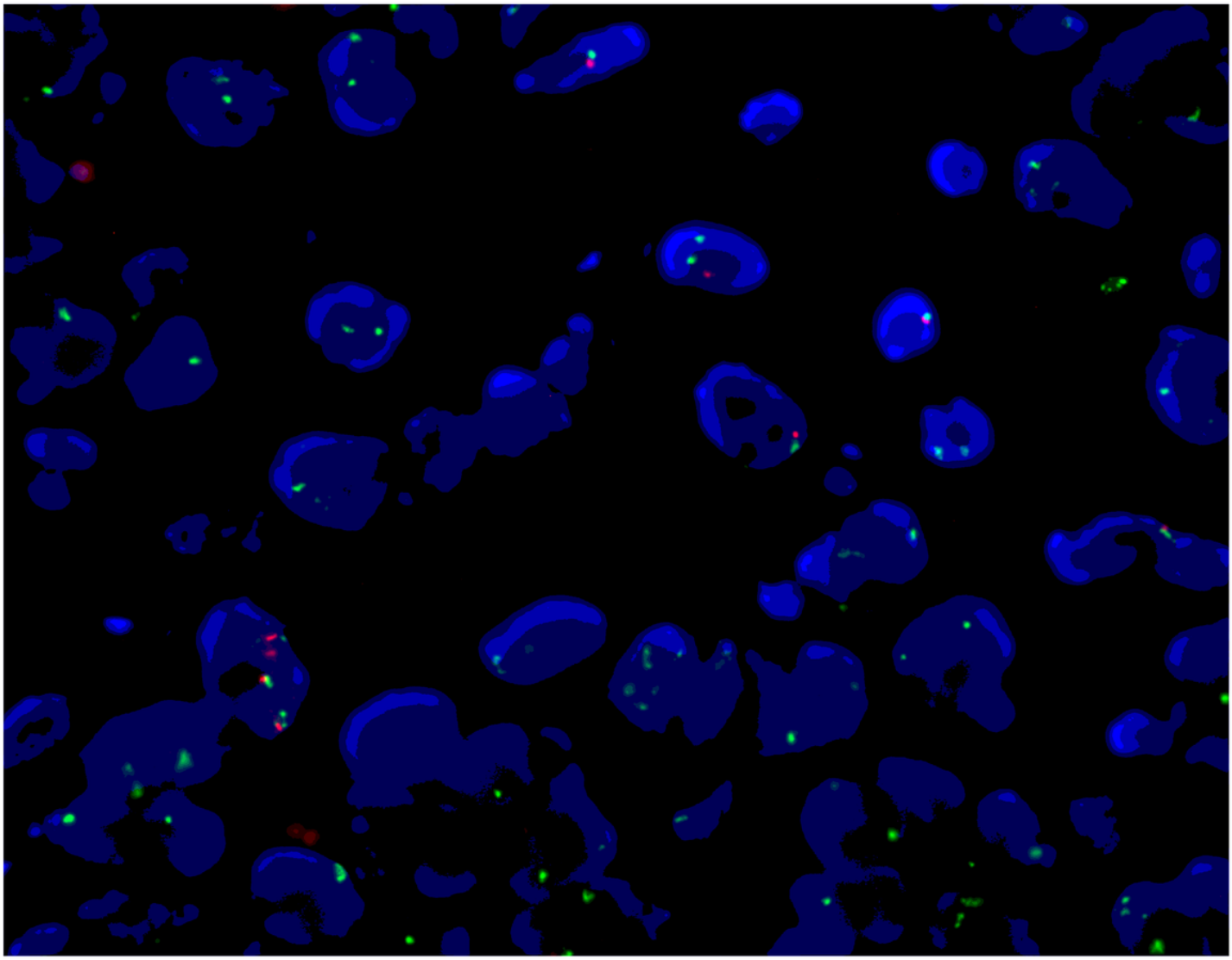

Figure 5

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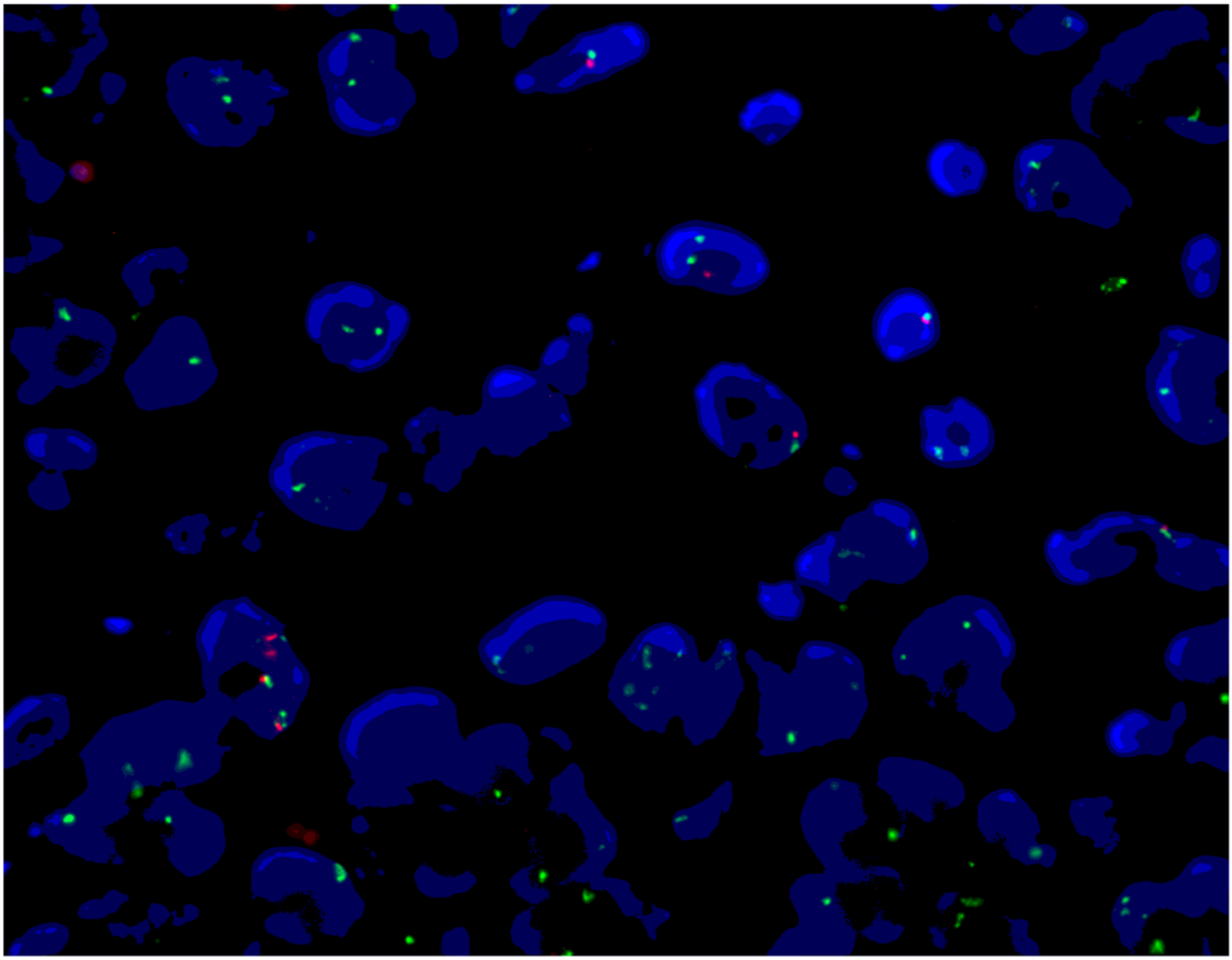

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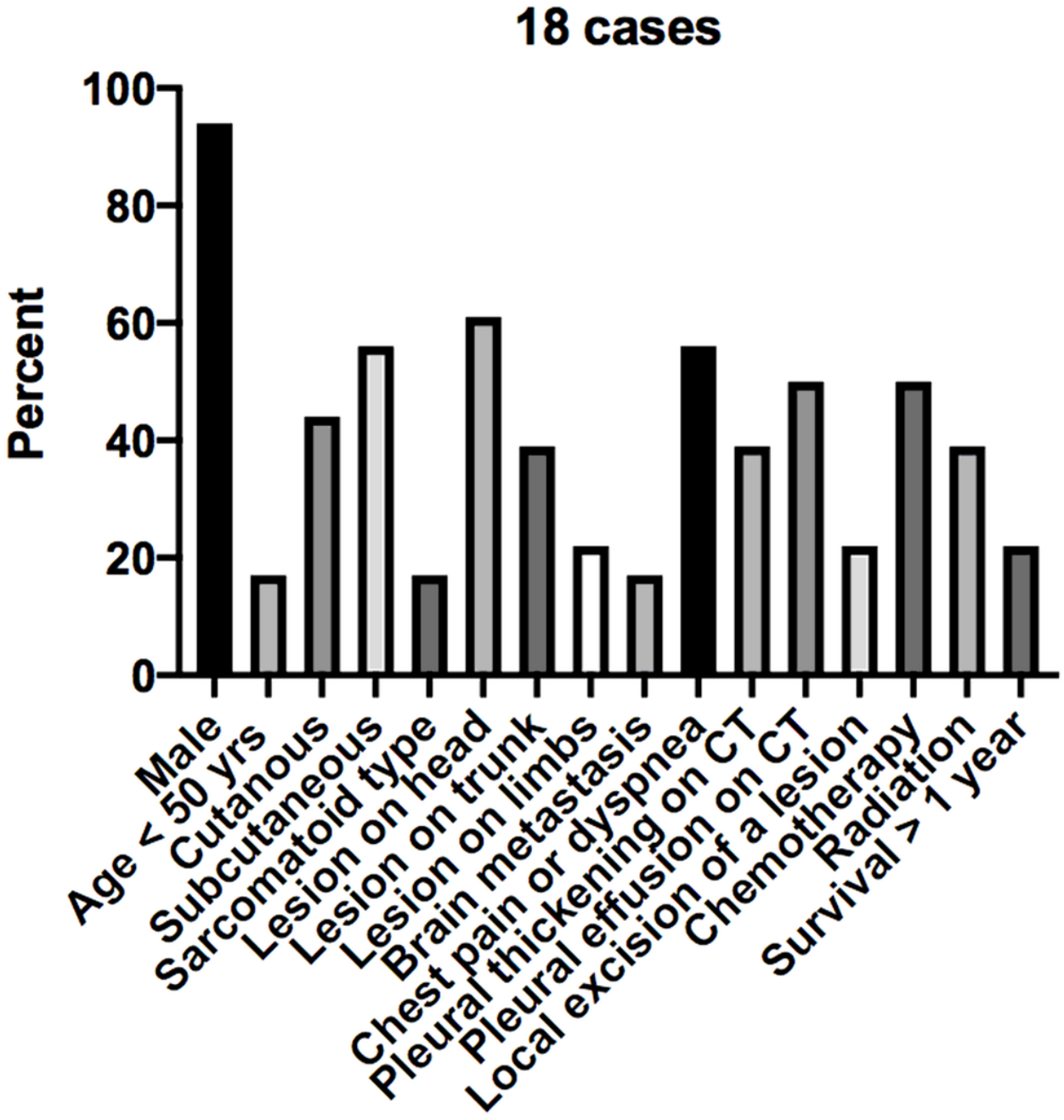

Figure 6

The statistical information of cutaneous or subcutaneous metastases from MM in the previous 18 cases including sex, location, distal metastasis, symptoms, CT features, interventions and prognosis.

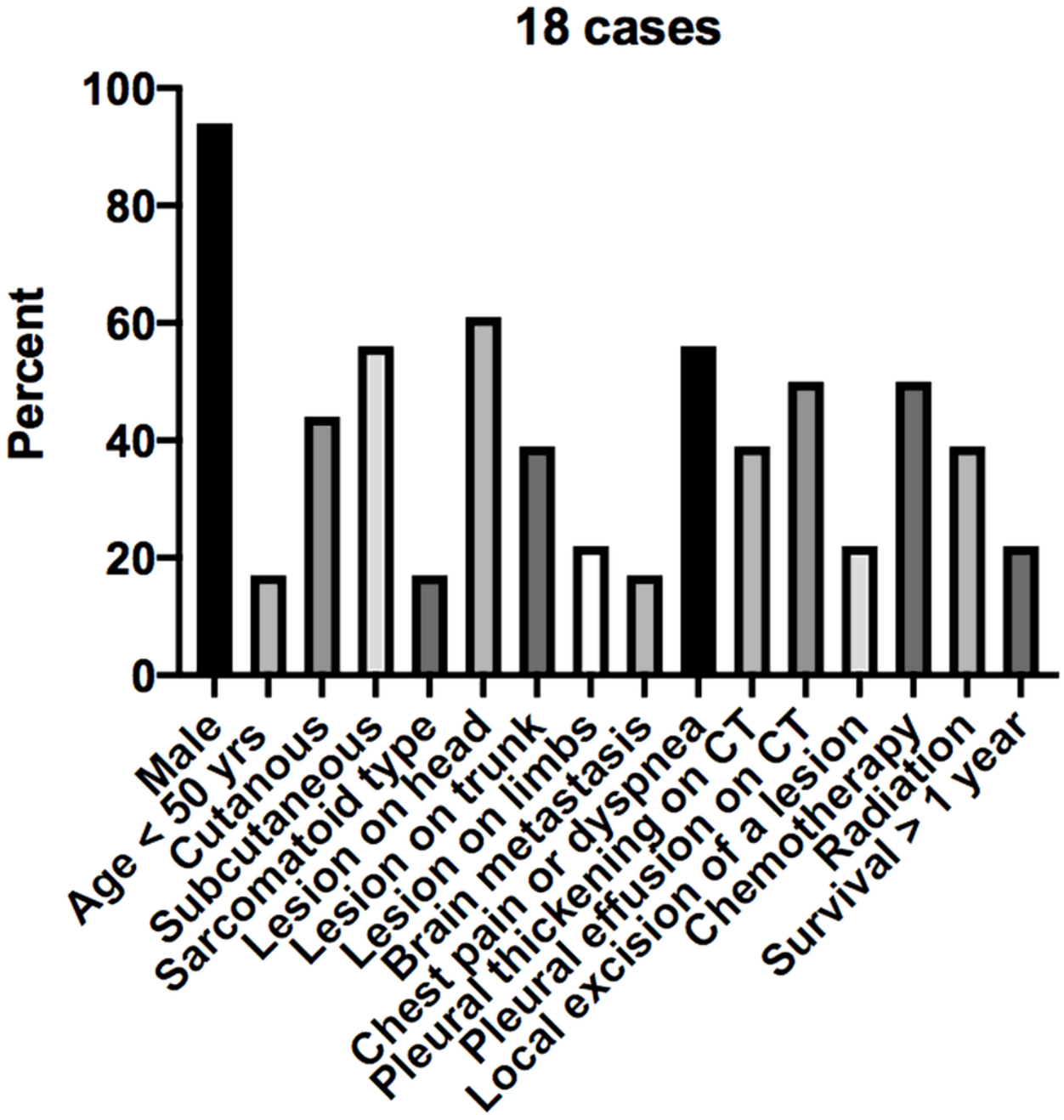

Figure 6

The statistical information of cutaneous or subcutaneous metastases from MM in the previous 18 cases including sex, location, distal metastasis, symptoms, CT features, interventions and prognosis.

Supplementary Files

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