

Undifferentiated Pleomorphic Sarcoma Of The Face: A Rare And Challenging Dermatologic Presentation

Zulfan¹, Eva Khrisna Sutedja², Endang Sutedja³, Kartika Ruchiattan⁴, Yuri Yogya⁵, Yogi Faldian⁶, Reiva Farah DwiYana⁷, Retno Hesty Maharani⁸

¹Department of Dermatology and Venereology, Faculty of Medicine, University Syiah Kuala, Dr. Zainoel Abidin Hospital, Banda Aceh, Indonesia

^{2,3,4,5,6,7,8}Department of Dermatology and Venereology, Faculty of Medicine, University Padjajaran, Dr. Hasan Sadikin Hospital, Bandung, Indonesia

Corresponding Author: Zulfan, e-mail: zulfan@usk.ac.id

Published: June, 2025

ABSTRACT

Undifferentiated pleomorphic sarcoma (UPS) is a rare and aggressive soft tissue malignancy, accounting for less than 1% of all soft tissue sarcomas. It is characterized by a high risk of metastasis and local recurrence, with diagnosis dependent on histopathological and immunohistochemical findings. This case report presents a rare instance of UPS and highlights the diagnostic complexity associated with its atypical presentation. A 48-year-old woman presented with pruritic, erythematous lesions on the forehead and a longstanding, hyperpigmented lesion on the left cheek. The forehead and ear lesions were unresponsive to topical treatments. Physical examination revealed multiple hyperpigmented macules and nodules with sanguine crusts. Histopathological examination showed a connective tissue stroma infiltrated by polymorphic cells, including lymphocytes, histiocytes, and plasma cells. Immunohistochemical analysis revealed focal positivity for CD31, CD34, CD68, and Ki-67, with negativity for CK, CD45, CD117, and Chromogranin. These findings were consistent with UPS. Radiologic imaging suggested pulmonary metastasis, and a secondary bacterial infection was identified. The patient was started on mupirocin for the secondary infection. Due to suspected pulmonary metastasis, surgical excision and radiotherapy were not pursued, and she began doxorubicin-based chemotherapy. Unfortunately, the patient passed away during the second cycle of chemotherapy. UPS is a rare and aggressive sarcoma that presents diagnostic challenges. Despite treatment, the prognosis remains poor due to its metastatic potential and limited response to conventional therapies.

Keywords: undifferentiated pleomorphic sarcoma, diagnostic challenges, immunohistochemistry

© The Author(s). 2021 Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0>

INTRODUCTION

Undifferentiated pleomorphic sarcoma (UPS) is a rare and aggressive soft tissue sarcoma (STS) characterized by a high risk of local recurrence and distant metastasis. Formerly referred to as malignant fibrous histiocytoma (MFH), the World Health Organization (WHO) reclassified it in 2013 as UPS, placing it under the category of undifferentiated soft tissue sarcoma (USTS), a group of pleomorphic stromal tumors lacking specific lines of differentiation (Allen, 2019; Baş, 2021; Kikuta et al., 2015).

Soft tissue sarcomas comprise less than 1% of all malignancies, with UPS being the fourth most common subtype, exhibiting an incidence of approximately 0.08–1 per 100,000 individuals (Allen, 2019). These tumors commonly arise in the extremities, retroperitoneum, viscera, and, less frequently,

the head and neck (Allen, 2019). Only about 10% of UPS cases occur in the head and neck region, accounting for less than 0.5% of all malignant neoplasms (Benites et al., 2020). Such rare anatomical presentations pose diagnostic challenges due to atypical clinical manifestations.

Histopathology examination is essential for diagnosing UPS, although its morphologic heterogeneity, often displaying a combination of storiform and pleomorphic patterns, can complicate identification (Araújo et al., 2022; Goldblum, 2014). Immunohistochemistry (IHC) serves as a critical adjunct, particularly in excluding other pleomorphic malignancies. UPS typically expresses markers consistent with myofibroblastic and fibroblastic differentiation, including positive smooth muscle actin staining (Karkos et al., 2016). Ki-67, a nuclear protein indicative of cellular proliferation, is frequently used as a prognostic biomarker in soft tissue sarcomas, including UPS, helping in the assessment of tumor aggressiveness (Campos et al., 2013).

Imaging plays a pivotal role in staging. Computed tomography (CT) is the initial recommended modality for evaluating local extension and detecting pulmonary metastasis (Sieg et al., 2016). Ultrasonography (USG) of the abdomen may be employed to assess for extrapulmonary spread, particularly to the retroperitoneum (Hong et al., 2021). In contrast, positron emission tomography (PET) is not routinely advised during initial staging, as it offers limited additional benefit in evaluating metastatic disease (Kikuta et al., 2015).

Given the rarity and nonspecific presentation of UPS, particularly in uncommon locations such as the head and neck, clinical suspicion is often low. Nevertheless, definitive diagnosis requires histopathological and immunohistochemical confirmation (Allen, 2019; Baş, 2021; Kikuta et al., 2015). This case report presents a rare instance of UPS and highlights the diagnostic complexity associated with its atypical presentation.

CASE ILLUSTRATION

A 48-year-old woman presented to the Department of Dermatology and Venereology at Dr. Hasan Sadikin General Hospital in Bandung, Indonesia, with a primary complaint of pruritic, erythematous lesions on the forehead. The symptoms began three months prior, initially appearing as small, button-sized spots that gradually thickened and extended to the left ear, exacerbated by sun exposure and scratching, and unresponsive to over-the-counter topical medications. Additionally, the patient reported a persistent, firm, blackish hyperpigmented lesion on the left cheek, progressively enlarging over the past ten years. The patient denied prior episodes of ulceration, bleeding, or exudation. Unlike the newer forehead and ear lesions, which began as erythematous papules, the cheek lesion was pigmented from onset and did not undergo color transition. Previous dermatological consultations resulted in treatment with antibiotics and topical anti-inflammatory agents, without clinical improvement. The patient had no personal or family history of skin cancer, autoimmune

disease, or genetic syndromes. There was no history of immunosuppression or chronic illness. The patient worked as a farmer with prolonged occupational sun exposure but no known chemical or industrial exposures.

Physical examination revealed stable vital signs and no signs of malnutrition. Dermatologic inspection identified multiple hyperpigmented macules and nodules with sanguine crusts on the cheeks [Figure 1]. The largest lesion measured approximately 2x2 cm, with an indurated and thickened texture on palpation, and ill-defined borders blending into the surrounding skin. Additional lesions were present on the forehead and behind the left ear, ranging in size from 1x1x0.2 cm to 2x1x0.03 cm, with clearer borders [Figure 1B]. Regional lymph node assessment found palpable regional lymphadenopathy in the submandibular area. A skin biopsy was performed for definitive diagnosis.

Gram staining of the lesion behind the ear revealed Gram-positive cocci, suggesting secondary infection. Histopathological examination of samples from the forehead and ear demonstrated a connective tissue stroma infiltrated by lymphocytes, histiocytes, and plasma cells. These cells exhibit condensed, polymorphic, and hyperchromatic nuclei, including spindle cells, vesicular nuclei, and occasional mitotic figures. However, the mitotic index was not quantified in the pathology report, limiting formal tumor grading. The sebaceous and eccrine glands of the forehead appeared histologically normal [Figures 2A and 2B]. The histological features were consistent with UPS, and IHC analysis was conducted for diagnostic confirmation. The tumor stained focally positive for CD31, a marker of blood vessels, suggesting vascular involvement, and showed high proliferative activity with Ki67, indicating a high rate of cell division. Additional tests were negative for cytokeratin (CK), ruling out epithelial cells; CD45 (leukocyte antigen), excluding blood cell origin; CD117 (c-kit), which rules out gastrointestinal stromal tumor; and Chromogranin, eliminating neuroendocrine tumors. The tumor was positive for CD34, indicating blood vessel cells, and CD68, pointing to the presence of histiocytes.

Further diagnostic evaluations included laboratory and radiologic studies. Complete blood count results were within normal limits. A chest radiograph revealed a reticular appearance in the right middle to the lower field, along with pleural thickening, findings suggestive of a secondary bacterial infection [Figure 3A]. Abdominal ultrasonography revealed no organomegaly or lymphadenopathy, and liver, gallbladder, pancreas, spleen, kidneys, and urinary bladder appeared unremarkable [Figure 3B]. Thoracic CT imaging showed nodules in the anterior centrilobular, posterior lobular, and inferior right pulmonary regions [Figure 4]. These nodules were considered suspicious for metastases originating from the suspected primary malignancy, although a pulmonary biopsy was not performed. Based on the clinical, histopathological, and radiologic findings, a final diagnosis of UPS with secondary bacterial infection and suspected pulmonary metastases was established.

The patient was prescribed mupirocin 2% cream for topical management of the secondary bacterial infection, to be applied twice daily to both cheeks. Due to the presence of suspected

pulmonary metastases, surgical excision and radiotherapy were not considered appropriate. The case was subsequently referred to the Internal Medicine Department for systemic chemotherapy. The patient was initiated on doxorubicin-based chemotherapy, planned for six cycles. Unfortunately, the patient passed away during the second cycle of treatment.

DISCUSSION

Undifferentiated pleomorphic sarcoma (UPS) is a rare neoplasm, classified among spindle cell tumors that originate in the skin or soft tissues. Despite sharing similar histopathological features, UPS can exhibit diverse clinical courses, complicating its diagnosis (Campos et al., 2013). The reclassification of MFH into USTS has highlighted the heterogeneous and polymorphic nature of these tumors, which lack a clear developmental pathway (Kikuta et al., 2015; Matushansky et al., 2009). Recent studies have suggested that mesenchymal stem cells, rather than histiocytes as previously thought, are the most likely origin of UPS (Baş, 2021; Goldblum, 2014).

The precise pathogenic mechanisms underlying UPS remain unclear. Generally, STSs are composed of heterogeneous mesenchymal cell populations that may arise through simple genetic mutations or complex genomic alterations (Widemann & Italiano, 2018). Some studies have suggested a potential link between UPS and environmental factors, such as sun exposure. Notably, a telomerase reverse transcriptase (TERT) mutation has been identified in 76% of skin-related UPS cases, highlighting the disease's molecular complexity (Robles-Tenorio & Solis-Ledesma, 2025; Widemann & Italiano, 2018).

Recent findings have also implicated a subpopulation of cells, termed side population (SP) cells, in UPS carcinogenesis. These SP cells, present in both normal and malignant tissues, are distinguished by their ability to efflux Hoechst dye (Robles-Tenorio & Solis-Ledesma, 2025). These cells exhibit stem-like properties, including self-renewal and tumorigenic potential, as demonstrated in xenograft models (Robles-Tenorio & Solis-Ledesma, 2025; Wang et al., 2012). Moreover, UPS-derived SP cells have shown significant activation of the Hedgehog and Notch signaling pathways, along with their downstream transcriptional targets. These molecular changes are consistently observed in both the tumor cells and the surrounding tissue, suggesting a critical role in UPS pathogenesis (Wang et al., 2012).

Soft tissue sarcomas (STSs) account for less than 1% of all cancers (Allen, 2019). These tumors typically arise in the extremities, retroperitoneum, viscera, and head and neck (Allen, 2019). UPS was previously reported to account for up to 40% of adult STS cases. While it typically presents in individuals between their fifth and seventh decades of life, with a slight male predominance, UPS can occur at any age (Oguri et al., 2018). A review of nine documented cases of primary gastric UPS

reported a mean patient age of 68 years (range: 42–79 years) and an 8:1 male-to-female ratio (Oguri et al., 2018).

For initial diagnosis, core needle biopsy is preferred over open incisional biopsy to establish the diagnosis of visceral UPS (Widemann & Italiano, 2018). Open biopsy should be performed by experienced surgeons to minimize the risks of bleeding and to preserve future resection planes. Fine-needle aspiration is generally not recommended due to its tendency to provide inadequate tissue samples (Robles-Tenorio & Solis-Ledesma, 2025). If initial results are inconclusive, image-guided core biopsy is advised. For deep thoracic, abdominal, or pelvic lesions, endoscopic needle biopsy is a feasible option (Robles-Tenorio & Solis-Ledesma, 2025). In cutaneous UPS, skin punch biopsy has been reported as an effective diagnostic method in several case studies (Robles-Tenorio & Solis-Ledesma, 2025; Wang et al., 2012).

Histopathologically, UPS can be categorized into pleomorphic, spindle cell, round cell, and epithelioid patterns (Cao et al., 2012). Storiform areas are characterized by plump spindle cells arranged around slit-like capillaries, forming a cartwheel-shaped pattern of short fascicles. Pleomorphic zones consist of larger fibroblastic cells, spherical histiocyte-like cells, and numerous large cells with hyperchromatic, irregular nuclei (Benites et al., 2020). While histological analysis aids in assessing tumor aggressiveness, the depth of UPS invasion is often a critical prognostic factor, particularly in advanced stages (Zhang et al., 2022). Deeper tissue infiltration is associated with higher recurrence and malignancy rates (Robles-Tenorio & Solis-Ledesma, 2025).

Additionally, IHC is pivotal in diagnosing UPS, a diagnosis of exclusion (Hornick, 2018). UPS typically lacks lineage-specific differentiation, making IHC an essential tool for ruling out mimickers (Sbaraglia et al., 2020). Negative staining for CK helps exclude epithelial neoplasms such as carcinomas. Similarly, the absence of CD45 rules out lymphoid malignancies, while a negative result for CD117 argues against gastrointestinal stromal tumors (GISTs). Chromogranin negativity eliminates neuroendocrine tumors from the differential diagnosis. In contrast, positive staining for CD68 supports histiocytic differentiation, and CD34 and focal CD31 positivity indicate some degree of vascular or mesenchymal lineage, features occasionally seen in UPS. A high Ki-67 proliferation index further reinforces the diagnosis by highlighting the aggressive mitotic activity characteristic of high-grade sarcomas (Hornick, 2018; Roland et al., 2016).

Metastatic potential in UPS varies, and prognosis is influenced by tumor size, anatomical site, resection margins, and metastatic spread (Simpson et al., 2009). The lungs are the most common metastatic site, consistent with the behavior of other STS.²³ Metastases may also occur in regional lymph nodes and other distant organs. Metastatic workup typically includes chest radiography, ultrasonography, or CT scans (Simpson et al., 2009; Stone & Buescher, 2005). Overall, the prognosis of

UPS is generally poor, particularly in metastatic cases, which may respond variably to chemotherapy (Simpson et al., 2009; Stone & Buescher, 2005).

CONCLUSION

Undifferentiated pleomorphic sarcoma (UPS) is a rare and challenging soft tissue sarcoma with diagnostic and treatment complexities. Histopathological and immunohistochemical evaluation is essential for accurate diagnosis. Due to its variable clinical course and poor prognosis, timely diagnosis and appropriate treatment, including surgery and chemotherapy, are crucial for managing the disease.

REFERENCES

- Allen, A. H. (2019). Large Undifferentiated Pleomorphic Sarcoma of the Posterior Thigh. *The American Journal of Case Reports*, 20, 318–322. <https://doi.org/10.12659/AJCR.914079>
- Araújo, E. P. dos S., Lima, S. C. V. da C., Galdino, O. A., Arrais, R. F., de Souza, K. S. C., & de Rezende, A. A. (2022). Association of CYP2R1 and VDR Polymorphisms with Metabolic Syndrome Components in Non-Diabetic Brazilian Adolescents. *Nutrients*, 14(21), 4612. <https://doi.org/10.3390/nu14214612>
- Baş, A. (2021). Undifferentiated pleomorphic sarcoma of skin in unusual locations: Report of two cases. *Joint Diseases and Related Surgery*, 32(1), 253–257. <https://doi.org/10.5606/ehc.2021.78856>
- Benites, B. M., Miranda-Silva, W., Fonseca, F. P., Oliveira, C. R. G. C. M. de, & Fregnani, E. R. (2020). Undifferentiated pleomorphic sarcoma of the mandible. *Journal of the Korean Association of Oral and Maxillofacial Surgeons*, 46(4), 282–287. <https://doi.org/10.5125/jkaoms.2020.46.4.282>
- Campos, M., De Campos, S. G. P., Ribeiro, G. G., Eguchi, F. C., Silva, S. R. M. Da, De Oliveira, C. Z., Da Costa, A. M., Curcelli, E. C., Nunes, M. C., Penna, V., & Longatto-Filho, A. (2013). Ki-67 and CD100 immunohistochemical expression is associated with local recurrence and poor prognosis in soft tissue sarcomas, respectively. *Oncology Letters*, 5(5), 1527–1535. <https://doi.org/10.3892/ol.2013.1226>
- Cao, X., Liu, J., Zheng, Y., Li, Q., Teng, Y., & Li, Y. (2012). Simultaneous squamous cell carcinoma with primary malignant fibrous histiocytoma of the larynx: A case report. *Molecular Medicine Reports*, 5(4), 971–973. <https://doi.org/10.3892/mmr.2012.775>
- Goldblum, J. R. (2014). An approach to pleomorphic sarcomas: can we subclassify, and does it matter? *Modern Pathology*, 27, S39–S46. <https://doi.org/10.1038/modpathol.2013.174>
- Hong, Z., England, P., Rhea, L., Hirbe, A., McDonald, D., & Cipriano, C. A. (2021). Patterns of Extrapulmonary Metastases in Sarcoma Surveillance. *Cancers*, 13(18), 4669. <https://doi.org/10.3390/cancers13184669>
- Hornick, J. L. (2018). Subclassification of pleomorphic sarcomas: How and why should we care? *Annals of Diagnostic Pathology*, 37, 118–124. <https://doi.org/10.1016/j.anndiagpath.2018.10.006>
- Karkos, P., Dova, S., Sotiriou, S., Markou, K., & Kostopoulos, I. (2016). Double primary malignant fibrous histiocytoma and squamous cell carcinoma of the larynx treated with laser laryngeal conservation surgery. *Ecancermedicalscience*, 10. <https://doi.org/10.3332/ecancer.2016.636>
- Kikuta, K., Morioka, H., Kawai, A., & Kondo, T. (2015). Global protein-expression profiling for

- reclassification of malignant fibrous histiocytoma. *Biochimica et Biophysica Acta (BBA) - Proteins and Proteomics*, 1854(6), 696–701. <https://doi.org/10.1016/j.bbapap.2014.08.012>
- Matushansky, I., Charytonowicz, E., Mills, J., Siddiqi, S., Hricik, T., & Cordon-Cardo, C. (2009). MFH classification: differentiating undifferentiated pleomorphic sarcoma in the 21st Century. *Expert Review of Anticancer Therapy*, 9(8), 1135–1144. <https://doi.org/10.1586/era.09.76>
- Oguri, Y., Cho, H., Oohinata, R., Onoyama, H., Takada, R., & Motoi, T. (2018). Aggressive undifferentiated pleomorphic sarcoma of the stomach involving long-term survival: A case report and literature review. *Molecular and Clinical Oncology*. <https://doi.org/10.3892/mco.2018.1739>
- Robles-Tenorio, A., & Solis-Ledesma, G. (2025). Undifferentiated Pleomorphic Sarcoma. In *StatPearls*. <https://doi.org/34033374>
- Roland, C. L., May, C. D., Watson, K. L., Al Sannaa, G. A., Dineen, S. P., Feig, R., Landers, S., Ingram, D. R., Wang, W.-L., Guadagnolo, B. A., Feig, B., Hunt, K. K., Cormier, J. N., Lazar, A. J., & Torres, K. E. (2016). Analysis of Clinical and Molecular Factors Impacting Oncologic Outcomes in Undifferentiated Pleomorphic Sarcoma. *Annals of Surgical Oncology*, 23(7), 2220–2228. <https://doi.org/10.1245/s10434-016-5115-5>
- Sbaraglia, M., Bellan, E., & Dei Tos, A. P. (2020). The 2020 WHO Classification of Soft Tissue Tumours: news and perspectives. *Pathologica*, 113(2), 70–84. <https://doi.org/10.32074/1591-951X-213>
- Sieg, E. P., Stepanyan, H., Payne, R., Fraunhoffer, E., Specht, C. S., Langan, S., & Rizk, E. (2016). Intraventricular Undifferentiated Pleomorphic Sarcoma: A Case Report. *Cureus*. <https://doi.org/10.7759/cureus.876>
- Simpson, E. L., Leung, D. Y. M., Eichen_eld, L. F., & Boguniewicz, M. (2009). Atopic Dermatitis. In S. Kang, M. Amagai, A. L. Bruckner, A. H. Enk, D. J. Margolis, A. J. McMichael, & J. S. Orringer (Eds.), *Fitzpatrick's Dermatology*. 9th ed. McGraw Hill.
- Stone, S. P., & Buescher, L. S. (2005). Life-threatening paraneoplastic cutaneous syndromes. *Clinics in Dermatology*, 23(3), 301–306. <https://doi.org/10.1016/j.clindermatol.2004.06.011>
- Wang, C. Y. Y., Wei, Q., Han, I., Sato, S., Azarnier, R. G., Whetstone, H., Poon, R., Hu, J., Zheng, F., Zhang, P., Wang, W., Wunder, J. S., & Alman, B. A. (2012). Hedgehog and Notch Signaling Regulate Self-Renewal of Undifferentiated Pleomorphic Sarcomas. *Cancer Research*, 72(4), 1013–1022. <https://doi.org/10.1158/0008-5472.CAN-11-2531>
- Widemann, B. C., & Italiano, A. (2018). Biology and Management of Undifferentiated Pleomorphic Sarcoma, Myxofibrosarcoma, and Malignant Peripheral Nerve Sheath Tumors: State of the Art and Perspectives. *Journal of Clinical Oncology*, 36(2), 160–167. <https://doi.org/10.1200/JCO.2017.75.3467>
- Zhang, S., Zhou, Z., & Xu, J. (2022). Undifferentiated pleomorphic sarcoma of the lateral thigh with KRAS/NF1 co-mutation recurred after repetitive surgical resection: A case report and review of the literature. *Frontiers in Surgery*, 9. <https://doi.org/10.3389/fsurg.2022.842054>

Figures Legends

Figure 1A-B

Physical examination findings. (A) Hyperpigmented macules observed on the cheek. (B) Hyperpigmented macules, nodules, and sanguine crusts on the forehead and behind the left ear. On palpation, the skin was hard and thick.



Figure 2 1A-B

Histopathology analysis of the forehead; (A) sebaceous glands and (B) eccrine glands. The epidermis is lined with stratified squamous epithelium, some of which was hyperplastic and keratinized, while the core remains within normal limits. The dermis consists of connective tissue stroma covered with inflammatory cells, including lymphocytes, histiocytes, and plasma cells. Among these, round, oval, and spindle-shaped cells show hyperplastic growth, with some exhibiting condensed, polymorphic, and hyperchromatic features. A few cells are vesicular with clear nuclei, and mitotic figures are observed (red arrows).

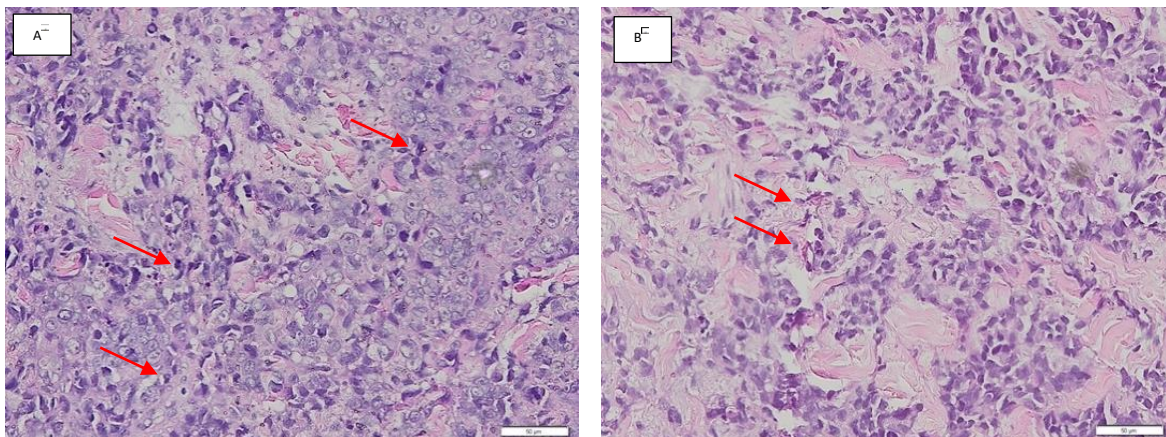


Figure 3 1A-B

Imaging findings of the patient. (A) Chest X-ray showing a reticular appearance in the right middle to lower field and left lower field, accompanied by pleural thickening, which may suggest a secondary bacterial infection. (B) Abdominal (USG) showing no evidence of metastasis.

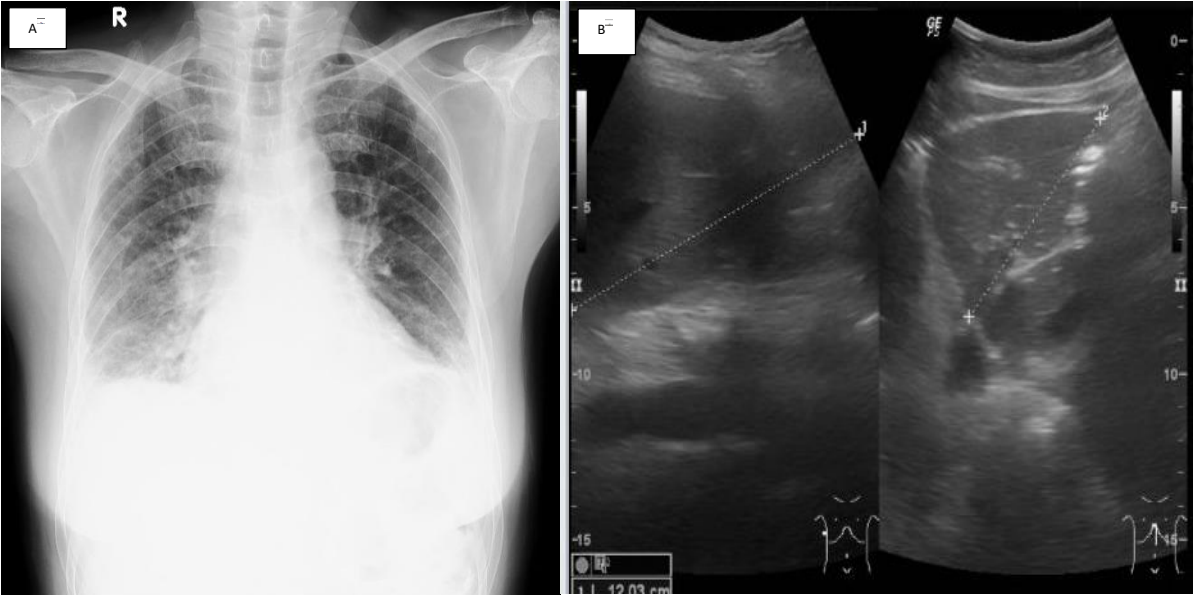


Figure 4 1A-B

Thoracic CT scan findings. (A) Anterior view showing a nodule in the centrilobular region. (B) Posterior and inferior views of the right lung (dexter pulmonary) showing the nodules (green arrow).

