Cutaneous lesions in a COVID-19 patient leading to a surprising diagnosis

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Shareable abstract (@ERSpublications)
Differential diagnosis of skin lesions is broad. Cutaneous metastases should always be considered in the appropriate clinical and laboratory context to ensure accurate diagnosis.
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A 60-year-old male patient was admitted to our hospital from a psychiatric clinic due to dyspnoea in April 2022, having been positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection for 12 days. The patient was treated according to the protocol for acute respiratory distress syndrome in coronavirus disease 2019 (COVID-19) infection, but he rapidly deteriorated, and eventually was intubated and transferred to the intensive care unit (ICU).

His past medical history was significant for hypertension, schizophrenia, dyslipidaemia, COPD, cholelithiasis, and ischaemic cardiomyopathy with anterior (2008) and inferior myocardial infarction (2019). He was a heavy smoker (60 pack-years smoking history) and fully vaccinated against COVID-19.

Upon arrival in the ICU, the patient was unstable, requiring haemodynamic and respiratory support. Physical examination was remarkable for at least two subcutaneous palpable lesions 1.5–2 cm in diameter, located on his torso (figure 1). Bedside imaging with chest radiography revealed a mass in the left lung middle zone (figure 2), while multiple hyperechoic liver lesions suggestive of metastases were detected with abdominal ultrasound. Additional imaging evaluation of these findings was not performed as the patient was unstable during his hospitalisation and transportation would not be safe.

Task 1

Based on the history and physical examination, the observed skin lesions could be attributed to which of the following?

a) Cutaneous manifestations of SARS-CoV-2 infection
b) Primary benign skin or soft tissue neoplasms
c) Primary malignant skin or soft tissue neoplasms
d) Metastatic skin cancer of unknown primary origin
e) All the above

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Histological examination of one of the subcutaneous nodules revealed diffuse infiltration of the dermis and subcutaneous fat by small cells with uniform nuclei, fine to granular nuclear chromatin and scant cytoplasm, with a high mitotic count (figure 3). The cells showed positive staining for the neuroendocrine markers CD56 (figure 4a) and synaptophysin (figure 4b).

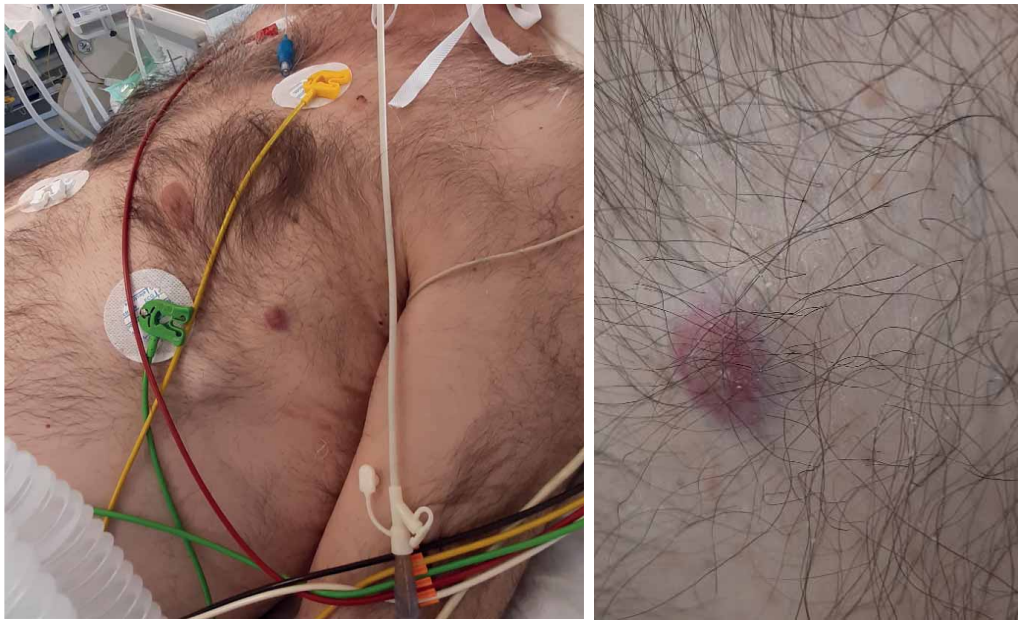

FIGURE 1 Subcutaneous palpable lesion.

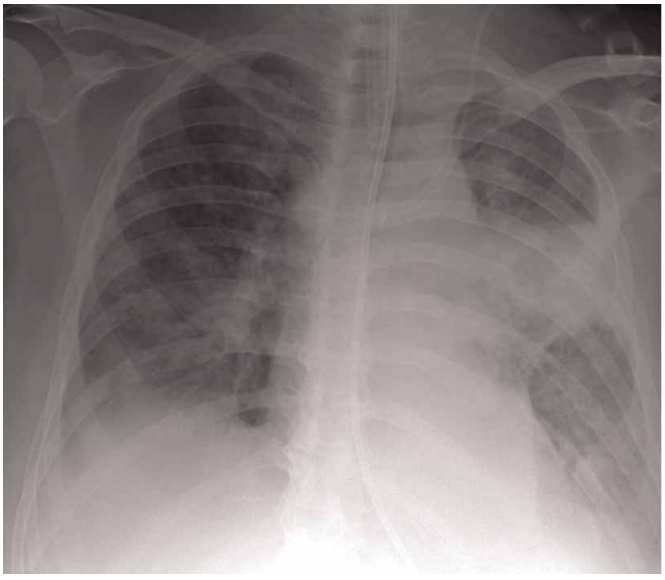

FIGURE 2 Chest radiograph revealing a mass in the left lung middle zone.

Task 2

Based on the morphological and immunohistochemical (IHC) findings, which of the following is the most probable diagnosis?

a) Adenocarcinoma
b) Neuroendocrine tumour
c) Squamous cell carcinoma
d) Sarcoma
e) Lymphoma
f) Melanoma

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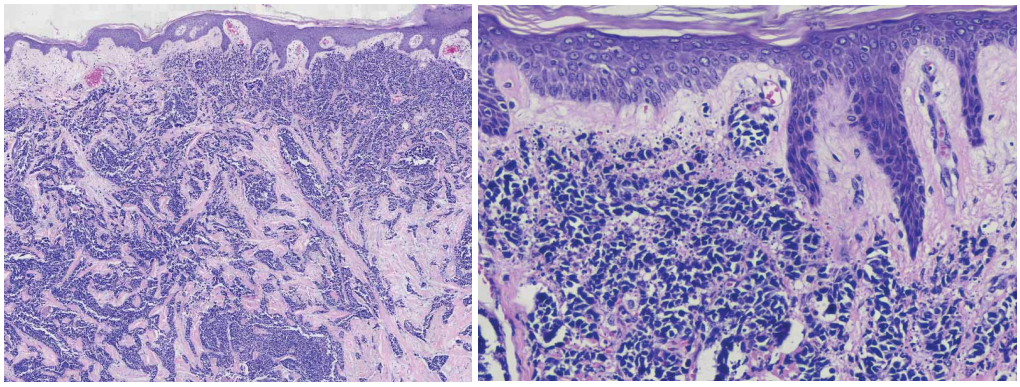

FIGURE 3 Haematoxylin and eosin (H&E) staining showing the cellular/nuclear features.

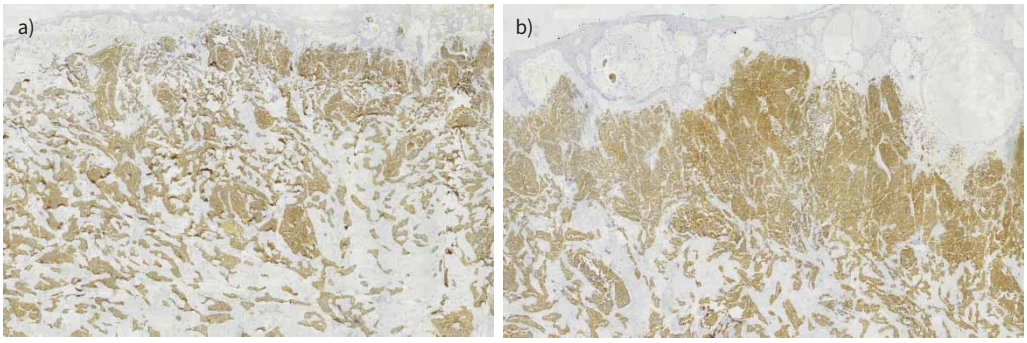

FIGURE 4 a) Positive staining for CD56. b) Positive staining for synaptophysin.

To reach a final diagnosis, additional IHC stains proved helpful. Apart from CD56 and synaptophysin, the cells were also positive for CKAE1/AE3 and thyroid transcription factor (TTF)-1 (figure 5). Staining for CDX-2, CA19-9, SOX-10, ALK, CD99, CD30, CD3, CD20, CK5/6, CK7 and Glypican-3 was negative.

Task 3

Based on the morphological/IHC findings, radiological findings, and the overall clinical presentation, which of the following is the most likely diagnosis in this patient?

a) Merkel cell carcinoma
b) Melanoma
c) Small cell lung cancer
d) Medullary thyroid cancer
e) Lung carcinoid tumour

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Unfortunately, the disease course was complicated with a hospital-acquired infection and despite appropriate treatment, the patient died after 24 days of hospitalisation.

Discussion

Lung cancer constitutes the leading cause of cancer-related mortality, with an annual incidence rate of 2.2 million cases. Nonsmall cell lung cancer (NSCLC) accounts for 85% of cases, with adenocarcinoma being the most common subtype, whereas SCLC comprises the remaining 15% of cases diagnosed [4]. Due to the aggressive nature of this malignancy, prompt diagnosis is essential in order to detect the disease at an early stage, before metastases have occurred, to maximise survival. Common sites of lung cancer metastasis include liver, brain, bones, lymph nodes and adrenal glands. Although uncommon, the skin can also be a site of lung metastasis, with the incidence rate ranging from 1% to 12%, according to the literature [5, 6]. Histopathologically, the most common lung cancer type identified is adenocarcinoma. SCLC, a neuroendocrine tumour, can also metastasise to the skin, indicating a poor prognosis [7–9].

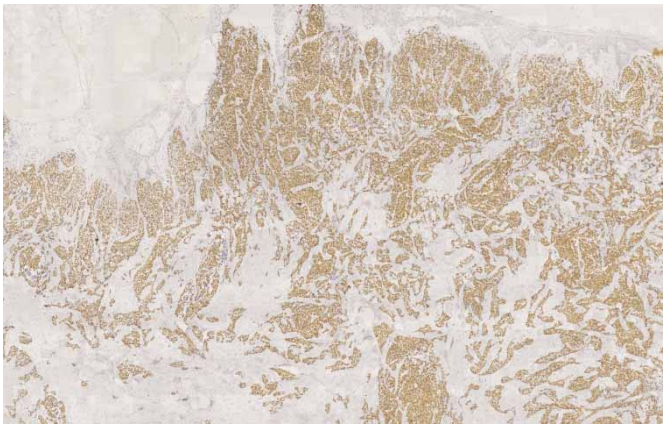

FIGURE 5 Positive staining for thyroid transcription factor-1.

A high index of clinical suspicion is required to characterise a skin lesion as a metastatic focus of lung cancer. Often, physicians attribute these skin lesions to common benign dermatological conditions, failing to make a prompt diagnosis. Even if malignancy is suspected, determination of the origin of malignancy may be challenging based on the clinical presentation alone, and primary skin cancer is usually first on the differential. Also, the absence of consistent and well-documented clinical features with which lung cancer metastasises to the skin may delay the diagnosis. Since the clinical picture alone is insufficient to characterise a skin lesion as metastatic lung cancer, implementation of other diagnostic tools is necessary. Biopsy of the skin lesion is easy, minimally invasive, relatively painless and valuable to determine the origin of the primary tumour and the most likely subtype. More specifically, when histology reveals cells of neuroendocrine origin, IHC can distinguish between SCLC and other NETs based on the positivity of various tumour markers. Of course, the clinical context in which the skin lesions appear can also reinforce the results of these laboratory techniques [3]. SCLC is a subtype of lung cancer that can rarely present with cutaneous metastases, and when histopathological and IHC findings point towards this diagnosis, effective treatment can be initiated.

In our case, the patient presented with signs and symptoms of SARS-CoV-2 infection, but careful inspection of the skin revealed lesions suspicious for malignancy. This finding, in conjunction with the chest radiograph that revealed a lung mass and an ultrasound that showed multiple hyperechoic hepatic lesions, raised concern regarding the malignant nature of the subcutaneous nodules. Biopsy of one of the lesions revealed findings that were suggestive of a NET, thus excluding lung adenocarcinoma and squamous cell carcinoma, as well as melanoma and lymphoma from the differential.

NETs constitute a heterogeneous tumour type that can arise from different organs. Histological evidence of small tumour cells with uniform nuclei and a fine to granular chromatic pattern alone is inadequate in delineating the primary origin of the tumour [2]. In our case, the skin lesions could be attributed to a primary NET of the skin, Merkel cell carcinoma, or metastatic NET with a primary origin in another organ. To differentiate between these two, specific IHC studies are required. In our case, the neoplastic cells were positive for CD56 and synaptophysin, which are sensitive markers of neuroendocrine origin, but not specific for a particular type of NET. TTF-1 is a nuclear transcription factor that is expressed mainly in the respiratory epithelium and the thyroid gland. Positive staining for this marker occurs in lung adenocarcinoma, SCLC, lung carcinoid tumour and medullary thyroid cancer. In such cases, the primary NET of the skin can be reliably excluded since it is negative for TTF-1. Lung adenocarcinoma was excluded as a likely diagnosis based on the histological and immunohistological findings (napsin A negative) [3, 10, 11]. Taking into consideration the patient's demographics, clinical presentation and imaging findings, carcinoid tumour and medullary thyroid cancer were excluded from the differential. Overall, SCLC emerged as the most likely diagnosis in our patient. Of note, although melanoma was unlikely based on the presence of neuroendocrine cells on biopsy, negative staining for SOX-10 ruled out this diagnosis.

The presence of cutaneous metastases in lung cancer signals a grim prognosis, and most patients have an estimated life expectancy of 5–6 months after their appearance. Their presence typically signifies late-stage disease, and treatment is mainly palliative. Appearance of lesions early in the disease course, as opposed to

later onset, as well as the presence of both cutaneous and extracutaneous metastases, negatively correlate with survival [6, 12].

The diagnostic pathway for advanced lung cancer patients is not always typical and can be challenging. Significant delays in obtaining biopsies due to concerns over the procedure (*e.g.* bronchoscopy, surgical tissue sampling), or healthcare system inefficiencies, are often reported [13], and eventually set back the initiation of treatment. This phenomenon becomes more prominent during increased workload in the healthcare system, as was the case with the COVID-19 pandemic. Significantly fewer cases of newly diagnosed cancer patients have been reported in healthcare systems worldwide. This could be attributed to the overlapping symptoms shared between SARS-CoV-2 infection and lung cancer in the context of hesitation exhibited by both healthcare professionals and patients to use healthcare resources out of fear of viral dispersion [14]. In the above setting, the diagnostic approach could be simplified if suspicious skin lesions are found. Thus, thorough clinical examination and careful evaluation of the findings is an important first step in the investigation pathway, that can clinch the most likely diagnosis.

It has been described in the literature that lung cancer patients are more prone to severe COVID-19. This may be due to factors related to healthcare system overutilisation, immunosuppression induced by the cancer itself and the accompanying treatment regimen, as well as risk factors for cancer that negatively impact on COVID-19 severity, such as smoking [15]. Challenges arise under these circumstances regarding the optimal treatment approach that should be sought, since management should be in accordance with the expected prognosis and potentially meaningful recovery. Our patient presented with severe SARS-CoV-2 infection and was eventually diagnosed with advanced-stage NSCLC. He was intubated and placed in the ICU, requiring intensive haemodynamic support. Although the benefits of continued treatment *versus* best supportive care were discussed in an effort to reach an appropriate consensus, given the patient's disease severity, treatment was never applied, as our patient died from a hospital-acquired infection.

Answer 1

e. Based on clinical presentation alone, the differential diagnosis is broad. SARS-CoV-2 may present with variable dermatological manifestations, including urticarial and vesicular rashes, macules, papules, purpuric lesions, and nodules [1]. Although subcutaneous nodules would be an atypical presentation of SARS-CoV-2, laboratory confirmation of COVID-19, as occurred in our case, should include this viral infection on the differential. Primary benign or malignant skin and soft tissue neoplasms can manifest with variable clinical features. The patient's heavy smoking history could also imply a primary lung malignancy that has metastasised to the skin. No definite diagnosis can be made at this point, and further investigations are warranted.

<< Go to Task 1

Answer 2

b. The presence of small tumour cells with uniform nuclei and a fine to granular chromatic pattern points towards the diagnosis of a neuroendocrine tumour (NET). Positive staining for CD56 and synaptophysin, which are sensitive markers of neuroendocrine origin, also reinforce this diagnosis. This patient's skin lesions could be attributed to a primary neuroendocrine carcinoma of the skin, or metastatic NET of an unknown primary origin [2].

<< Go to Task 2

Answer 3

c. The most likely diagnosis is small cell lung cancer (SCLC). TTF-1 is positive in SCLC, medullary thyroid cancer, lung adenocarcinoma, and lung carcinoid tumour, but not in Merkel cell carcinoma or other extrapulmonary NETs [3]. Although carcinoid tumour could be a possible diagnosis based on the IHC findings, it mainly presents in younger individuals. Based on the presence of the lung mass on chest radiography, and multiple lesions in the liver, likely indicating metastatic spread, medullary thyroid cancer is unlikely. Melanoma would not stain positive for TTF-1, and histology would not reveal neuroendocrine features. When trying to differentiate between a primary NET of the skin and metastasis spread of a NET to the skin, TTF-1 expression is useful in making this distinction. Consideration of the patient's clinical features and radiographic imaging can also point to the most likely diagnosis. All the lymphocytic markers were negative, so the diagnosis of lymphoma was excluded.

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Conflict of interest: The authors have nothing to disclose.

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