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CASE REPORT

Neuroendocrine Tumour of the Lung: A Diagnostic Challenge

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ABSTRACT

This is a case of a 62-year-old Indian man who was diagnosed with a rare type of lung neuroendocrine tumour (NET) of atypical carcinoid (AC) subtype which comprises only 0.1%–0.2% of pulmonary neoplasms. He initially presented to a private hospital in May 2018 with a 6-month history of chronic productive cough and haemoptysis. Chest X-Ray (CXR), CT scan, bronchoscopy, biopsy and broncho-alveolar lavage were conducted. At this stage, imaging and histopathological investigations were negative for malignancy. Diagnosis of bronchiectasis was made and he was treated with antibiotic and tranexamic acid. Due to financial difficulties, his care was transferred to a university respiratory clinic in June 2018. His condition was monitored with CXR at every visit and treatment with tranexamic acid was continued for 6 months. However, due to persistent haemoptysis, he presented to the university primary care clinic in Dec 2018. Investigations were repeated in January 2019 where his CXR showed increased opacity of the left retrocardiac region and CT scan revealed a left lower lobe endobronchial mass causing collapse with mediastinal lymphadenopathy suggestive of malignancy. Bronchoscopy, biopsy and histopathology confirmed the presence of NET. Although the Ki-67 index was low, the mitotic count, presence of necrosis and evidence of liver metastases favoured the diagnosis of AC. A positron emission tomography Ga-68 DONATOC scan showed evidence of somatostatin receptor avid known primary malignancy in the lungs with suspicions of liver metastasis. He was subsequently referred to the oncology team and chemotherapy was initiated. This case highlights the challenge in diagnosis and management of patients with AC. Physicians ought to be vigilant and have a high index of suspicion in patients who present with persistent symptoms on multiple visits. Early diagnosis of NET would prevent metastasis and provide better prognosis. Continuous follow-up shared care between primary care and secondary care physicians is also essential to provide ongoing psychosocial support for patients with NET, especially those with metastatic disease.

KEYWORDS: Neuroendocrine tumor, diagnostic challenge, primary care

INTRODUCTION

Lung cancer is the most common cancer in the world attributing to 1.8 million new cases and 1.6 million deaths per year [1]. Approximately 30% - 40% of these cases occur in developing countries [1]. In Malaysia, lung cancer was the second most common cancer among males and fifth among females [2]. The incidence increased with age with a peak at the age of 70 years and above [2].

Symptoms of a primary lung tumour include cough, haemoptysis, chest pain, or shortness of breath.

Some patients may present with hoarseness and non-specific symptoms, such as weight loss or fatigue. Other symptoms such as headache, seizure, personality change, pain as well as pathologic fractures should also be assessed as patient may present late with symptoms of distant metastasis. Risk factors such as smoking history, exposure to environmental toxins such as asbestos, radiation and passive smoking should be explored during history taking.

Unfortunately, most lung cancer cases in Malaysia presented late [3]. Approximately 75% - 88%

of cases were diagnosed in advanced stages of III or IV, where palliative therapy was the only option [3]. Only 12% presented early where curative surgical resection could be offered [3]. Failure to recognize symptoms and patient beliefs in traditional complementary medicine were common reasons for the delay in the diagnosis [3].

Lung neuroendocrine tumours (NET) comprise a special subgroup of lung cancer where only 25% represent primary lung neoplasms and the remaining 75% composed of non–small cell carcinoma (NSCLC) [4]. Of the primary lung NET, 20% were small cell lung cancer (SCLC), 3% were large cell neuroendocrine carcinoma (LCNEC), 2% were typical carcinoid (TC) and 0.2% were atypical carcinoid (AC) [4]. A recent update by the World Health Organization (WHO) on Classification of Lung Tumours recommended new diagnostic criteria for lung NET on the basis of histopathologic features, including cell size, cell morphologic features, mitotic index, architectural growth patterns, and presence of necrosis [5]. Accurate histopathologic classification of lung NET can be challenging, particularly with small volume of diagnostic tissue. However, this step is critical to determine appropriate treatment options for the patients.

Evidence on the optimal treatment strategies for lung NET is still lacking due to their heterogeneous nature, rarity and the lack of randomized trials [6]. Surgery remains the only curative option for patients with localized TC or AC. Surgical resection provides excellent outcomes for TC, with 5- and 10-year survival rates of 90% and 80%, respectively, and very low recurrence rates of 3% - 5%. The recurrence rate for AC is much higher at 25%, with a lower 5- and 10-year survival rates following surgery at 70% and 50%, respectively [6].

In this report, we present an extremely rare case of lung NET of AC subtype. The elusive nature of this malignant tumour presents diagnostic and management challenge to physicians.

CASE PRESENTATION

A 62-year-old gentleman presented to a private hospital in May 2018 with a 6-month history of productive chronic cough with yellow sputum. This was associated with episodes of haemoptysis where he coughed up approximately 2-3 spoonful of blood per day which was mixed with sputum. However, there was no loss of weight, loss of appetite, fever, breathlessness, orthopnoea, paroxysmal nocturnal dyspnea, chest pain, cutaneous flushing, diarrhea or wheezing. He quit smoking 3 years ago with a 40-year history of smoking 20 cigarettes per day. His medical history includes sinusitis, gastritis, hypertension and hyperlipidaemia. He used to work as an attendant at a petrol station for 5 years and subsequently became a contractor for more than 20 years.

On examination, he was not tachypnoeic and able to speak in full sentences. There was presence of finger clubbing and coarse crepitation over the left lower zone. CT scan showed intrabronchial lesion in the left lower basal segments, most likely due to mucous plugging in keeping with bronchiectasis. Bronchoscopy showed a mucoid-looking mass at the opening of left bronchus occluding the opening. Histopathology of the left bronchus biopsy revealed chronic inflammation with predominantly foamy macrophages and fibrin. Smears of bronchoalveolar (BAL) aspirate were cellular, composed mainly of benign bronchial cells and alveolar macrophages. There was no atypical cells presence. It was negative for mycobacteria or malignancy. BAL culture showed mixed growth of 3 types of organisms. He was subsequently treated as bronchiectasis with mucous plugging with a course of antibiotic and tranexamic acid.

Due to financial constraint, this patient requested to be transferred to a university respiratory clinic for continuation of care in June 2018. He was diagnosed as bronchiectasis with a differential diagnosis of pan bronchiolitis. He subsequently came for regular follow up with chest x-ray (CXR) being performed at each visit to monitor progression of the lung lesions. The episodes of haemoptysis were still persistent with 1 spoonful, 2-3 episodes per week. CXR showed persistent air space infiltrates over left lower zone of the lung and there was no new consolidation. He was treated with tranexamic acid 500mg three times daily for symptomatic treatment.

However, due to the increasing amount of haemoptysis, he presented as a walk-in patient at the university primary care clinic in December 2018, about

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6 months after being followed up at the university respiratory clinic. At the primary care clinic, he was treated symptomatically with the same dosage of tranexamic acid for a week. There was no investigation ordered at this stage.

One month later in January 2019, he presented again to the primary care clinic due to worsening symptoms. On examination, his vital signs were stable. Auscultation of the lungs revealed reduced air entry over left lower zones with coarse crepitation. CXR was repeated and there was a presence of increased opacity over cardiac silhouette as compared to the previous ones. CT scan of the lung was done urgently and it showed a heterogeneous enhancing mass obliterating the left lower bronchus causing collapse of the entire left lower lobe with multiple mediastinal lymphadenopathy suggestive of malignancy. This is shown in Figure 1.

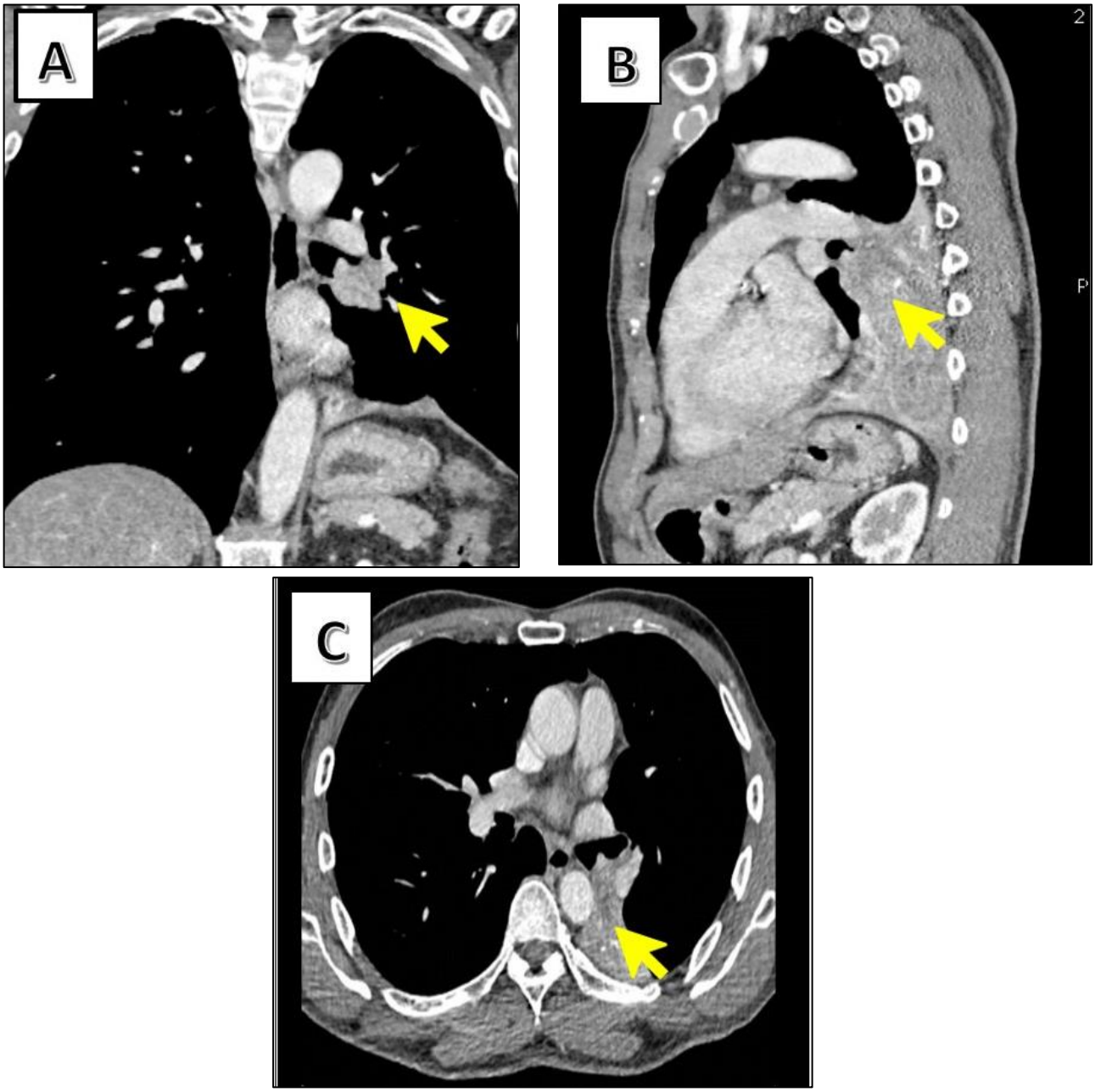

Figure 1 Selected CT thorax on coronal view (A), sagittal view (B) and axial view (C) demonstrating an enhancing mass obliterating the left lower lobe bronchus causing collapse of the left lower lobe with mediastinal lymphadenopathy suggestive of malignancy.

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He was urgently referred to the respiratory clinic where bronchoscopy was repeated. Histopathology examinations showed neuroendocrine tumour with Ki-67 proliferation index < 2 suggestive of typical carcinoid (TC). However, due to the mitotic count, presence of necrosis and evidence of liver metastases, the diagnosis of atypical carcinoid (AC) was made. The tumour cells were arranged in clusters with some pseudo-glandular spaces as shown in Figure 2 and 3. They exhibited monotonous round to oval nuclei with fine granular chromatin. Two mitotic figures were seen in high power fields. Figure 4 shows immunohistochemistry stain with positive cytokeratin, chromogranin A, synaptophysin and CD 56. His serum chromogranin A was high with a value of 770ng/mL (normal value: 27-94 ng/mL) and negative for TTF-1.

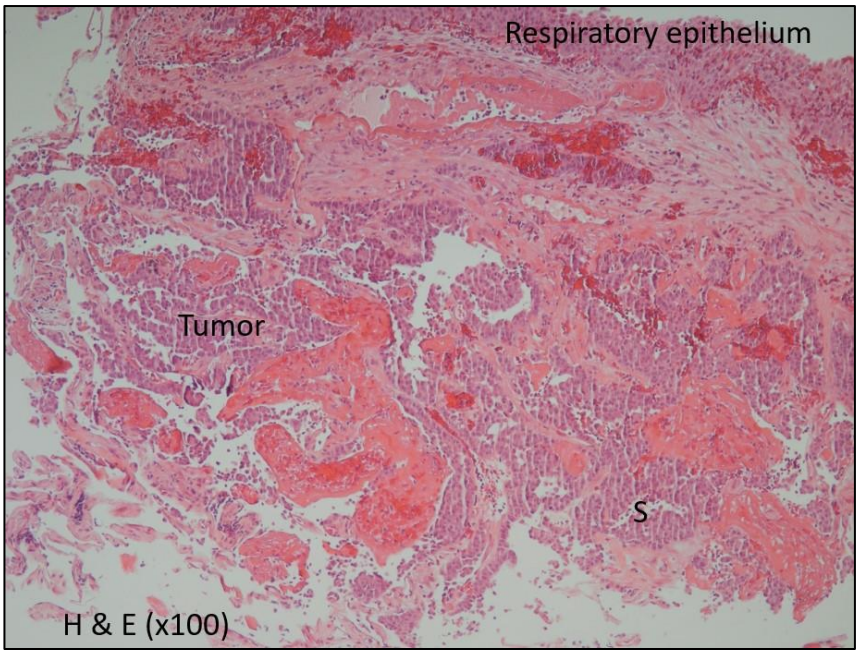

Figure 2 Haematoxylin & eosin (H&E) stain of endobronchial biopsy showing tumour cells arranged in clusters with some pseudoglandular space (S). Part of covering respiratory epithelium seen at upper right. H&E x100.

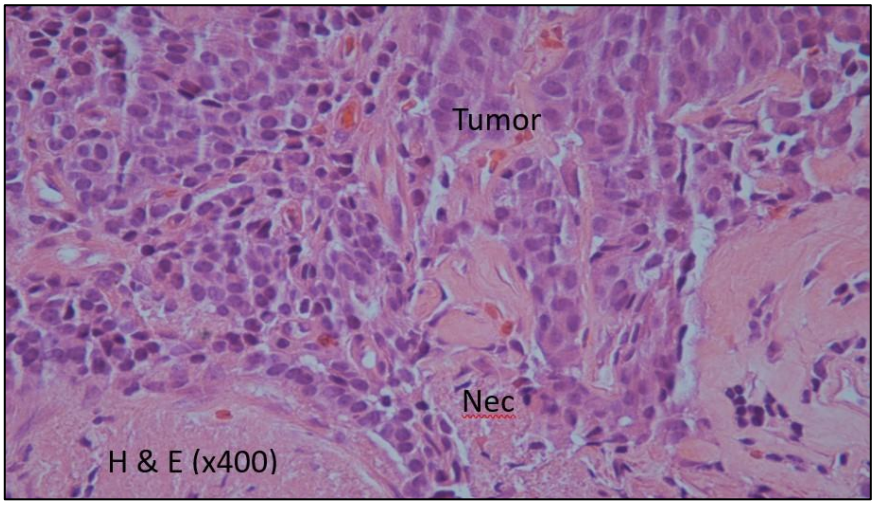

Figure 3 Haematoxylin & eosin (H&E) stain of endobronchial biopsy showing tumour cells exhibit monotonous round to oval nuclei with necrosis (Nec). H&E x400.

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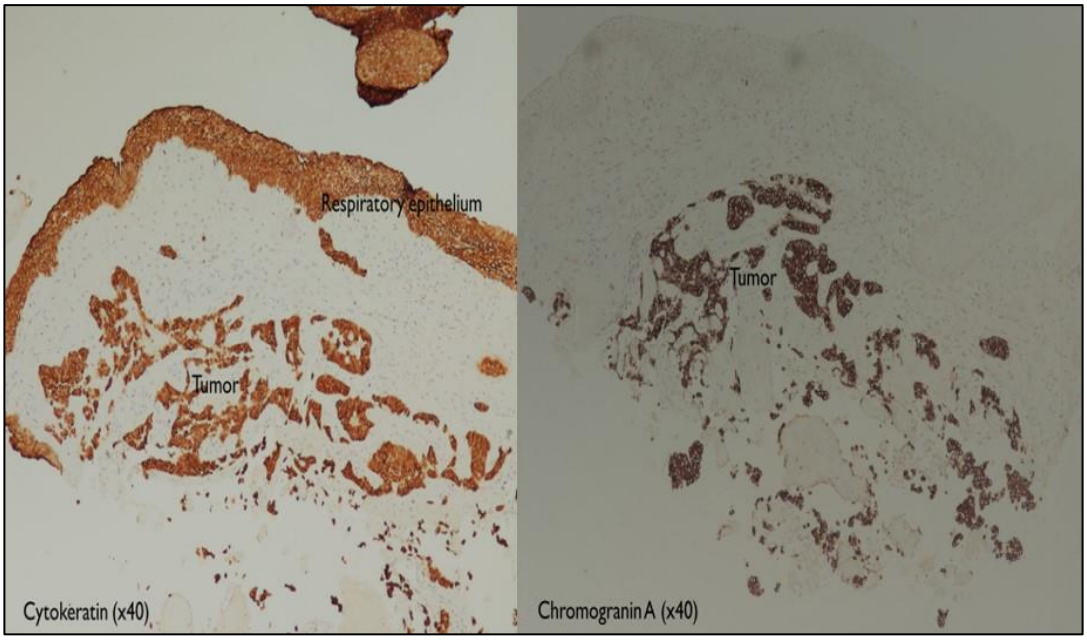

Figure 4 Immunohistochemistry (IHC) stains showing positivity for cytokeratin (left) and chromogranin A (right). IHC x 40.

A positron emission tomography (PET) scan was performed for staging of the NET. It showed heterogenous Ga-68 DONATOC uptake at soft tissue mass in the left lower lobe involving the bronchus measuring about 5.8cm X 6.3cm X 4.5cm. There was also focus of Ga-68 DONATOC uptake seen at segment V of the liver. These were evidence of somatostatin receptor avid confirming primary malignancy in the lungs with suspicion of liver metastasis.

His case was discussed in a multidisciplinary meeting which involved respiratory physician, radiologist, histopathologist, cardiothoracic surgeon as well as oncologist. This patient was then referred to an oncology unit for chemotherapy as he was not a candidate for lung resection. He is currently on regular follow up with respiratory clinic, primary care clinic as well as oncology clinic. His episode of haemoptysis has stopped completely after the second cycle of etoposide+cisplatin chemotherapy regime. He is scheduled for restaging of the tumour after completing the third cycle of etoposide.

DISCUSSION

Neuroendocrine tumours are considered very rare, although its prevalence was reported to have increased over the last 3 decades [7]. This is thought to be due to greater awareness of the disease, better detection methods and diagnostic protocols [6]. Unfortunately, there is limited epidemiological data of lung NET in Malaysia or Asia due to its rarity.

The diagnosis and management of lung NET is challenging due to the variation in natural history, non-specific symptoms and limited high-level evidence from large randomized trials [8]. Approximately 50% of patients are usually asymptomatic at the time of diagnosis [8]. They can present with cough, haemoptysis, dyspnoea and chest pain or symptoms that mimic more common conditions such as asthma, chronic obstructive pulmonary disease and pneumonia [8]. It is also worth to note that secretory type of lung NET can present with cutaneous flushing, diarrhoea, and wheezing caused by excessive secretion of hormones and peptides by tumour cells [8].

Due to the variations in clinical history of NET, malignancy would only be suspected after initial treatment fails to improve symptoms, hence delaying diagnosis by months or years [7, 8]. Reflecting on our patient, he presented with prolonged productive cough with haemoptysis. There was no loss of weight, loss of appetite or shortness of breath. The initial investigations conducted at the private hospital which included a CT scan, bronchoscopy and histopathology examinations did not reveal any malignancy, making the diagnosis of lung cancer unfavorable at that stage. He was diagnosed to have bronchiectasis and was treated symptomatically. However, a high index of suspicion is

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necessary to proceed with prompt reinvestigations in patients who present with multiple visits. An opportunity was missed at the first visit to the primary care clinic, as he was not thoroughly investigated despite presenting with worsening haemoptysis. It is crucial to identify red flags at every primary care consultation, as early diagnosis of malignancy would provide better prognosis, improve quality of life and reduce anxiety [9].

Clinically, approximately 20%–40% of patients with TC or AC were nonsmokers and they usually occur in younger age group with a mean age of 45-50 years [4]. In contrast, majority of patients with SCLC and LCNEC were heavy cigarette smokers and they typically occur predominantly in older patients with a mean age of 65 years [4]. Interestingly, in this case report, the patient is a 62-year-old man with a strong history of cigarette smoking that fits more towards high grade tumours. AC in this age group is extremely rare [4]. A similar case was reported in a female smoker where the initial diagnosis was LCNEC [10]. However, the diagnosis was revised several times over the course of her illness due to the atypical behavior of the tumour [10]. The diagnosis of AC was eventually confirmed with histopathological examination of her scalp biopsy, 13 months after the initial presentation [10].

In managing NET, it is pivotal for the physician to differentiate between low grade (TC), intermediate grade (AC) and high grade (LCNEC and SCLC) NET. The prognosis and management are different between these groups. The 5-year survival rate ranges from around 87% for patients with TC and AC, to 2% for patients with LCNEC and SCLC [9]. Although NET are slow growing tumours, advanced disease leads to poor survival [7]. In patients with well-differentiated NET with distant metastasis, 73% would die within 5 years [7]. It was unfortunate that in this case, CT scan and histopathology conducted during his first presentation was negative for malignancy. This was probably due to difficulty in obtaining adequate sample during biopsy and BAL. Subsequently, during staging, there was already evidence of metastases to the liver which would have a negative impact on his prognosis.

Histopathologic tumour classification has the greatest impact on prognosis and treatment in lung NET. Therefore, accurate classification is crucial. Microscopically, the definitive diagnostic criteria to differentiate AC from TC are mitotic count and necrosis with TC showing < 2 mitoses/ $2mm^2$ and absence of necrosis, while AC showing 2-10 mitoses/ $2mm^2$ or presence of necrosis [11]. Assessment of the Ki67 labeling index is not part of the classification of lung NET, however it would be useful to separate well-differentiated NET (carcinoid tumours) from poorly differentiated (high grade) neuroendocrine carcinomas on biopsy specimens [11]. As proposed by a grading system based on the combination of Ki-67, mitotic count, and necrosis, TC and AC often have a low Ki-67 labeling index [8]. The cutoff values for grade 1 is <4%, grade 2 are 4%-24% and grade 3 is ≥25% [8]. In this patient, the tumour shows low Ki-67, however the mitotic count and presence of necrosis was in keeping with AC.

Accurate classification of the NET and the identification of the neuroendocrine phenotype should include the evaluation of specific neuroendocrine markers. Chromogranin A (CgA) and synaptophysin expression are the most reliable stains (8, 11). Other markers which are useful to define a neuroendocrine phenotype include PGP 9.5, neuron-specific enolase (NSE) and CD56 [11]. Out of these, synaptophysin is regarded as one of the most specific markers of neuroendocrine differentiation, with higher sensitivity than CgA or NSE [11]. Serum CgA is recommended to be used to monitor tumour recurrence or treatment response, as it often correlates with tumour size [11]. In relation to our patient, immunohistochemistry stain showed positive for cytokeratin, synaptophysin and CD 56 with serum CgA about 8 times more than the normal value making the diagnosis of NET very likely.

Nuclear medicine plays a vital role in the assessment of tumour localization, tumour size and invasion as well as metastasis for subsequent patient management. The nuclear medicine method of choice in diagnosing NET is the somatostatin receptor-based radionuclide imaging [12]. Somatostatin (SST) receptors are expressed in majority (80%) of the lung NET [12]. In this imaging technique, the binding of a radiolabeled ligand to the somatostatin receptor is the mechanism of action [12]. Over the past 10 years, the introduction of positron emission tomography (PET) with the 68Ga-labeled octreotide derivatives

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DOTATOC and DOTATATE have revolutionized NET diagnosis [12]. This relatively new technology demonstrated a sensitivity of more than 90% and a specificity of almost 100% in the diagnosis of NET [12]. In this patient, there was heterogenous Ga-68 DONATOC uptake at soft tissue mass in the left lower lobe involving the bronchus measuring about 5.8cm X 6.3cm X 4.5cm with metastases at segment V of the liver.

In patients with lung NET, the decision to commence therapy is recommended based on a number of clinical and pathological factors including symptoms, tumour grade, comorbidities and organ functions [13, 14]. The more aggressive nature of AC tumours prompted clinicians to administer adjuvant chemotherapy based on evidence showing a response rate of 20% to chemotherapy [14]. Regimens showing antitumour activity against lung NET include doxorubicin/capecitabine, everolimus + cisplatin, octreotide, everolimus + octreotide, and etoposide + cisplatin [14]. However, due to small number of patients with lung NET, evidence for optimal treatment strategies is still lacking [14].

For patient with AC, close follow-up at 3 to 6 months intervals is recommended [13, 14]. However, follow-up visits and imaging need to be personalized depending on the individual's baseline status, new symptoms and if treatment modification is contemplated. More detailed guidelines are needed to guide management and long term care for patients with NET.

CONCLUSION

In summary, this is a case of AC, an extremely rare NET occurring in an elderly patient with history of cigarette smoking. The diagnosis, investigation and management of lung NET are complex due to the variation in natural history, non-specific symptoms and limited high-level evidence from large randomized trials. It is important for primary care physicians to have a high index of suspicions in patients presenting with persistent symptoms and multiple visits. Understanding the elusive nature of NET is also important to identify the red flags as this will lead to prompt investigations, early detection, early referral and hence early management. This knowledge is also helpful in educating the patient and family with regards to treatment and prognosis. Due to its complex nature, multidisciplinary management involving primary care physician, clinical oncologist, endocrinologist, radiologist, pathologist, and surgeon is pivotal in providing long term comprehensive and coordinated care for patients with NET. This approach has shown clear advantages including better diagnostic and staging accuracy, reduction in diagnosis and treatment delays, and improved adherence to evidence-based therapy [13, 14]. Continuous follow-up shared care between primary care and secondary care physicians is also essential to provide ongoing psychosocial support for patients with NET, especially those with metastatic disease.

Conflict of Interest

Authors declare none.

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REFERENCES

1. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2015; 136[5]:E359-E86.
2. Abdul Manan A ITN, Abdullah NH, Zainal Abidin A, Wahab M. Malaysian National Cancer Registry Report. MOH/P/IKN/0116 (AR), 2007-2011.
3. Kan CS, Chan KM. A Review of Lung Cancer Research in Malaysia. Med J Malaysia. 2016; 71(Suppl 1):70-8.
4. Rekhtman N. Neuroendocrine Tumors of the Lung: An Update. Arch Pathol Lab Med. 2010; 134[11]:1628-38.
5. Travis WD, Brambilla E, Nicholson AG, Yatabe Y, Austin JHM, Beasley MB, et al. The 2015 World Health Organization Classification of Lung Tumors: Impact of Genetic, Clinical and Radiologic

Vol 4(2) (2019) 97-104 | jchs-medicine.uitm.edu.my | eISSN 0127-984X
https://doi.org/10.24191/jchs.v4i2.7550

Advances since the 2004 Classification. J Thorac Oncol. 2015; 10[9]:1243-60.
6. Öberg K, Hellman P, Ferolla P, Papotti M, Group obotEGW. Neuroendocrine Bronchial and Thymic Tumors: ESMO Clinical Practice Guidelines for Diagnosis, Treatment and Follow-up. Ann Oncol. 2012; 23(Suppl 7):vii120-vii3.
7. Yao JC, Hassan M, Phan A, Dagohoy C, Leary C, Mares JE, et al. One Hundred Years after "Carcinoid": Epidemiology of and Prognostic Factors for Neuroendocrine Tumors in 35,825 Cases in the United States. J Clin Oncol. 2008; 26(18):3063-72.
8. Wolin EM. Challenges in the Diagnosis and Management of Well-Differentiated Neuroendocrine Tumors of the Lung (Typical and Atypical Carcinoid): Current Status and Future Considerations. Oncologist. 2015; 20[10]:1123-31.
9. Fisseler-Eckhoff A, Demes M. Neuroendocrine Tumors of the Lung. Cancers. 2012; 4[3]:777-98.
10. Derks JL, Speel E-JM, Thunnissen E, van Suylen RJ, Buikhuisen WA, van Velthuysen M-LF, et al. Neuroendocrine Cancer of the Lung: A Diagnostic Puzzle. J Thorac Oncol. 2016; 11[3]:e35-e8.
11. Naidoo J, Santos-Zabala ML, Lyriboz T, Woo KM, Sima CS, Fiore JJ, et al. Large Cell Neuroendocrine Carcinoma of the Lung: Clinico-Pathologic Features, Treatment, and Outcomes. Clin Lung Cancer. 2016; 17[5]:e121-e9.
12. Yang J, Kan Y, Ge BH, Yuan L, Li C, Zhao W. Diagnostic Role of Gallium-68 DOTATOC and Gallium-68 DOTATATE PET in patients with Neuroendocrine Tumors: a Meta-Analysis. Acta Radiol. 2014; 55[4]:389-98.
13. Phan AT, Oberg K, Choi J, Harrison LH, Jr., Hassan MM, Strosberg JR, et al. NANETS Consensus Guideline for the Diagnosis and Management of Neuroendocrine Tumors: Well-Differentiated Neuroendocrine Tumors of the Thorax (includes Lung and Thymus). Pancreas. 2010; 39[6]:784-98.
14. Chong CR, Wirth LJ, Nishino M, Chen AB, Sholl LM, Kulke MH, et al. Chemotherapy for Locally Advanced and Metastatic Pulmonary Carcinoid Tumors. Lung Cancer. 2014; 86[2]:241-6.

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