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甲状腺功能亢进介导肺癌超进展病例报告

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摘 要

目的：分析甲状腺功能亢进与恶性肿瘤发生发展之间的关系。方法：回顾性分析1例甲状腺功能亢进介导肺癌超进展的患者并复习相关文献。结果：本例老年男性患者，因“咳嗽、咳痰、气促2年余，再发加重3月”入院。既往糖尿病史10年余，甲亢病史5年余，未规律诊治。患者肺部CT平扫不排除肿瘤病变，后经支气管镜活检，结合免疫组化结果，考虑小细胞肺癌。对比其外院2月余前胸部CT结果，考虑肺癌超进展。结论：甲状腺功能亢进可提高肺癌发生发展的易感性。临床医生在诊疗过程中，应加强对甲亢与癌症关联的认识，提高甲亢患者的风险意识，并对癌症患者进行早期识别和明确诊断，以提高患者预后。

关键词

甲状腺功能亢进，肺癌，超进展

Case Report of Hyperprogression of Lung Cancer Mediated by Hyperthyroidism

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Abstract

Objective: To analyze the relationship between hyperthyroidism and the occurrence and devel-

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opment of malignant tumors. Methods: A retrospective analysis was conducted on a case of hyperthyroidism-mediated ultra-progressive lung cancer, along with a review of relevant literature. Result: In this case, an elderly male patient was admitted due to "coughing, expectoration, and dyspnea for over 2 years, exacerbated for 3 months". He had a medical history of diabetes for more than 10 years and a history of hyperthyroidism for over 5 years, which had not been managed consistently. Pulmonary CT scan suggested possible tumor lesions. Subsequently, bronchoscopic biopsy in combination with immunohistochemical results led to a consideration of small cell lung cancer. Comparing the chest CT findings from over 2 months ago at another hospital, it was concluded that the patient's lung cancer had undergone ultra-progressive growth. Conclusion: Hyperthyroidism can increase susceptibility to the occurrence and progression of lung cancer. Clinicians should enhance their understanding of the association between hyperthyroidism and cancer during the diagnostic process, raise awareness of the risk among patients with hyperthyroidism, and ensure early recognition and definitive diagnosis of malignancy in these patients, thereby improving patient prognosis.

Keywords

Hyperthyroidism, Lung Cancer, Hyperprogression

1. 引言

甲状腺功能亢进症(甲亢)是一种内分泌疾病，其特征是甲状腺激素(主要是三碘甲状腺原氨酸 T3 和四碘甲状腺原氨酸 T4)过度合成和分泌引起神经、循环、消化等多个系统功能亢进。在全球碘充足国家中，甲亢的患病率估计在 0.2%~2.5%之间[1]。

癌症是全球第二大致死原因[2]。有研究表明，大约 40%的癌症病例是可以预防的[3]，这提示了早期识别癌症风险因素的重要性。

甲状腺激素与恶性肿瘤之间的关联早一个多世纪前首次被提出[4]。不少研究表明，当甲状腺激素缺乏时，实体瘤的生长速度会减缓，而甲状腺激素增多则会增加肿瘤的生长速度。Krashin 等人[5]总结了 2019 年以前关于甲状腺激素和癌症关系研究的相关文献：在 90 篇临床前研究的相关文献中，其中 15 项研究发现甲减可减缓肿瘤生长速度，54 项研究表明甲状腺激素对癌症的发生发展具有促进作用；在 86 篇临床研究的相关文献中，分别有 36 项、45 项研究提示甲减对肿瘤的抑制作用及甲状腺激素对肿瘤的促进影响。然而，目前甲状腺激素是否可作为一种可改变的癌症风险因素仍有一定争议。本研究就 1 例甲亢介导肺癌超进展患者的临床特点及发病机制进行分析，结合相关文献，以加强临床医师对甲亢与癌症关系的认识。

2. 病例报告

男性患者，63 岁，因“咳嗽、咳痰、气促 2 年余，再发加重 3 月”于 2023-07-06 日来诊。患者 2 年前无明显诱因出现咳嗽、咳白色粘稠痰，偶有活动后气促、胸闷，无胸痛，间断至外院就诊，考虑肺气肿，予药物治疗(具体诊疗过程及用药不详)症状稍缓解，但仍反复。3 月余前患者感咳嗽、咳痰较前加重，频率较前增多，伴明显活动后气促、胸闷，伴乏力、纳差、体重下降，遂就诊于外院，诊断慢性阻塞性

肺疾病。外院予抗感染、祛痰平喘、氧疗等处理，患者症状仍反复，自觉气促、乏力加重，表现为行走约 100 m 需停下休息，轻度体力活动受限，遂就诊于我院。患者自患病以来，精神、睡眠尚可，胃纳欠佳，自觉小便增多，伴尿急，大便正常。近 2 月体重下降 5 Kg。既往糖尿病 10 余年，甲亢 5 年余，未规律药物治疗。吸烟 20 支/天，饮酒 3~4 次/月，每次约 1~5 两。母亲患有哮喘，兄弟姐妹患有糖尿病。

入院查体：T：36.2℃，P：119 次/分，R：24 次/分，BP：135/77 mmHg，神清，体型消瘦，全身皮肤黏膜未见明显出血点及瘀斑。浅表淋巴结未触及肿大。双肺呼吸音粗，未闻及明显干、湿性啰音。心律齐，各瓣膜听诊区未闻及杂音。腹软，全腹部无压痛及反跳痛。双下肢未见水肿。

入院相关检查：甲状腺功能测定五项 B (含抗体)：抗甲状腺球蛋白抗体 0.22 IU/mL (0~4)，抗甲状腺过氧化物酶抗体 94.44 IU/mL (0~9)，游离三碘甲状原氨酸 18.86 pmol/L (3.09~7.42)，游离甲状腺素 71.25 pmol/L (7.64~16.03)，促甲状腺刺激激素 0.002 mIU/L (0.38~5.33)。呼吸道肿瘤三项(癌胚抗原、神经元特异性烯醇化酶、鳞状细胞癌相关抗原)、病毒全套、呼吸道感染病原体检测(包括甲乙流和腺病毒) + 结合杆菌抗体测定未见明显异常。痰涂片可见少量革兰阳性球菌及少量革兰阴性杆菌，未见真菌及分枝杆菌。肺通气功能检查+舒张实验(2023-07-06)：中度阻塞性通气功能障碍，MVV 占预计值 63.2%。舒张试验阳性。FeNO：9 ppb，CaNO：10.5 ppb。胸部 CT 平扫显示(2023-07-06) (图 1)：右肺门影增大，右主支气管管腔变窄，右肺下叶多发斑片影，纵隔多发肿大淋巴结，肿瘤性病变需考虑，建议增强扫描。支气管镜活检病理(2023-07-14)显示(图 2)：镜下见少量支气管粘膜挤压变形明显，粘膜下见巢片状小蓝细胞弥漫

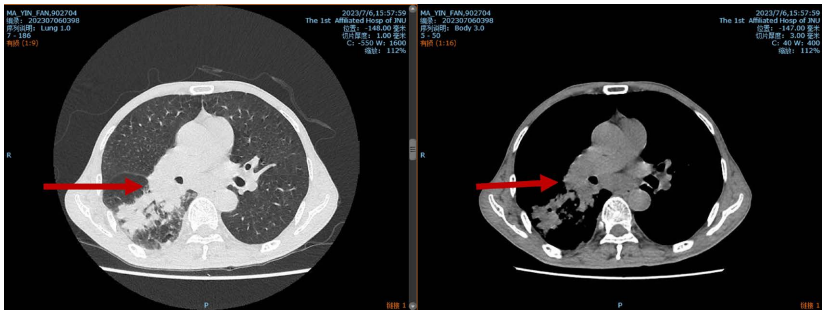

Figure 1. Chest CT Image from July 6, 2023. Enlargement of the right hilum, narrowing of the lumen of the right main bronchus, multiple patchy opacities in the right lower lobe, multiple enlarged mediastinal lymph nodes, and consideration of neoplastic lesions is warranted
图 1. 2023-07-06 胸部 CT 图像，右肺门影增大，右主支气管管腔变窄，右肺下叶多发斑片影，纵隔多发肿大淋巴结，肿瘤性病变需考虑

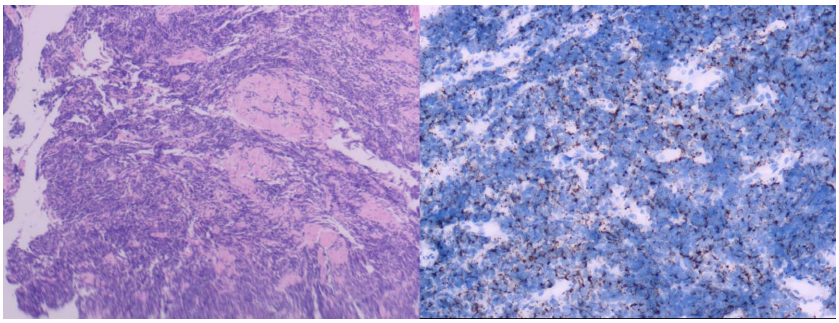

Figure 2. Bronchoscopy Biopsy Pathology Image from July 14, 2023. Under the microscope, there is evident compression deformation of a small amount of bronchial mucosa, with diffuse infiltration by nests of small blue cells in the submucosa, accompanied by visible mitotic figures
图 2. 2023-07-14 支气管镜活检病理图像，镜下见少量支气管粘膜挤压变形明显，粘膜下见巢片状小蓝细胞弥漫浸润，可见核分裂像

浸润，可见核分裂像；免疫组化：CK7 (+)，TTF-1 (+)，CEA (−)，Syn (−)，CgA (+)，CD56 (+)，P53 (−)，RB (弱+)，INSM-1 (小灶+)，P40 (−)，Ki-67 约 80% (+)；结合组织形态及免疫组化，符合：小细胞肺癌。对比患者外院胸部 CT (2023-04-15)结果(图 3)，考虑肺癌超进展。

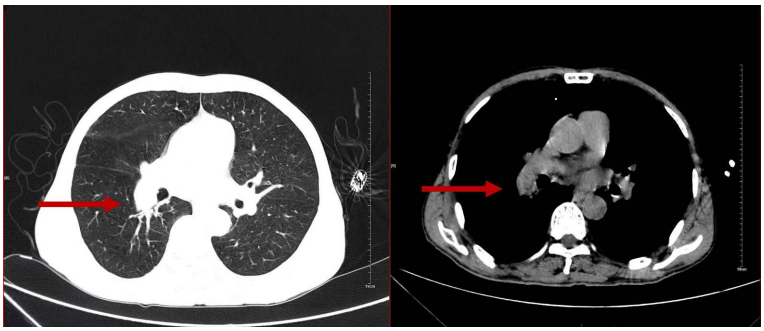

Figure 3. Chest CT image from April 15, 2023
图 3. 2023-04-15 胸部 CT 图像

3. 讨论

结合上述病例，63 岁男性，因咳嗽、咳痰、气促 2 年余，再发加重 3 月入院，既往糖尿病、甲亢病史，未规律治疗。患者胸部 CT 不排除肿瘤可能，后经支气管镜活检，诊断小细胞肺癌。结合其 2 月余前外院胸部 CT 结果，考虑甲状腺功能亢进介导肺癌超进展。

甲亢最主要的特征是甲状腺激素的过度合成和分泌。甲状腺激素(TH)包括三碘甲状腺原氨酸(T3)和甲状腺素(T4)，其与恶性肿瘤之间的关联在 1896 年首次被提出[4]。此后，大量的体内、体外及人群研究均提示甲状腺激素具有刺激肿瘤发生的作用，包括肺癌、乳腺癌、胃肠道癌、血液癌、前列腺癌和黑色素瘤等[6] [7] [8] [9]。Yeh [10]等人对 17,033 名新诊断的甲亢患者进行了一项大型前瞻性研究，并使用 34,066 名非甲亢患者的匹配队列作为比较集体，研究发现，在 4 年随访期间，甲亢与癌症发病风险增加相关(校正 HR 1.20)，此外，甲亢的持续时间越长，患癌症的风险就越大。Hellevik 等人在对将近 3 万名个体进行的长达 9 年的前瞻性研究中发现，低促甲状腺激素水平(TSH < 0.5 mu/L，暗示有亚临床甲状腺功能亢进)可增加特定癌症类型的风险，特别是肺癌(HR 2.60)和前列腺癌(HR 1.96) [11]。相对应的，甲状腺功能减退可能会延缓癌症的发病或降低其侵袭性[12] [13] [14]。有研究表明，甲减患者乳腺癌的确诊年龄比正常人大 7 岁[13] [14]，而肺癌则大 9 岁[15]。

然而，TH 影响非甲状腺肿瘤发生发展的具体分子学机制目前仍不明确。一些研究表明，甲状腺激素可以作用于细胞膜表面整合素家族中的 $\alpha_v\beta_3$ 受体，并激活丝裂原活化蛋白激酶(MAPK)信号转导通路，从而诱导血管生成和肿瘤细胞增殖[16] [17] [18]。此外，糖酵解和三羧酸循环可通过代谢产物的生物合成来支持肿瘤生长[19] [20]。相关研究表明，代谢物(如琥珀酸盐、富马酸盐和 2-羟基戊二酸)在异常积累时也会促进肿瘤的发生[21]。由于甲状腺激素在细胞代谢中起着重要作用，甲状腺激素也有可能通过细胞代谢影响肺癌的发生发展。

甲状腺激素对恶性肿瘤的影响强调了控制甲亢病情的重要性，然而，由于治疗时间较长，部分患者容易忽视其危害,淡化了自我管理意识。美国甲状腺协会(ATA)的一项共识声明建议[22]，对于无癌症症状且血清促甲状腺激素(TSH)浓度轻度高于正常参考范围的非癌性患者，可以暂时不进行甲状腺激素替代治疗。这强调了甲亢患者控制 TH 水平的重要性。临床医生应加强甲亢与癌症关联的认识，加强甲亢患者自我管理意识，对甲亢合并癌症患者做到综合管理。

4. 结论

目前，甲状腺功能亢进对肺癌进展的影响，仍需要进一步研究。临床医生在癌症患者的诊疗过程中，应适当筛查是否有潜在的甲状腺疾病[23]，同时需强调快速建立甲状腺功能正常的重要性，以降低甲亢对新发和现有癌症的患者产生不利影响的风险。对癌症患者及患癌高危人群亦可适当增加影像学评估的频率，做到早期诊断和综合治疗。

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