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CASE STUDY

The link between thyroid hormones and cutaneous squamous cell carcinoma

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This case study aims to improve clinical practice by highlighting hypothyroidism as a possible risk factor for the development of squamous cell carcinoma (SCC), particularly in people of colour. A 65-year-old Black female presented with generalised weakness and confusion. Examination revealed a left-sided oculomotor nerve palsy. Laboratory tests indicated central hypothyroidism with a CT brain scan showing a cystic lesion in the suprasellar region. Patient history revealed that a malignant growth had been excised from her left leg eight months earlier and biopsy results revealed SCC. This case study underlines the connection between hypothyroidism and SCC, emphasising the complex role of thyroid hormones in cancer development.

Keywords: thyroid hormones, cutaneous squamous cell carcinoma, hypothyroidism

Case report

A 65-year-old Black female was brought to the emergency centre with a history (~1 year) of generalised body weakness and occasional confusion. The family described that the patient was previously independent and capable of performing all the activities of daily living but had steadily declined in her ability to do so. They confirmed that she had deviated from her cognitive baseline and reported a history of lethargy and occasional confusion. The patient's family had assumed that the initial symptoms observed were attributed to age but expressed concern due to the significant worsening of her symptoms in the last six weeks. A general examination revealed an area of mild hypopigmentation on the left leg with no other skin lesions noted. The thyroid examination was within normal limits and no stigma of immunecompromised state or chronic disease was observed. A focused neurological examination revealed an isolated left-sided oculomotor nerve palsy. The rest of the physical examination was unremarkable. Noteworthy patient history included a skin lesion on the left lower leg eight months prior. The histological biopsy revealed a malignant neoplasm characterised by malignant cells growing in large nests and surrounded by fibrosis, the borders of which had infiltrated 14 mm into the reticular dermis. The entire tumour, measuring 130 ×15 ×25 mm was completely excised with good margins and had healed well.

The patient was admitted, and special investigations included a delirium workup. Included in this were thyroid function tests for thyroid stimulating hormone (TSH) and thyroxine (T4), vitamin B_{12}, urea and electrolytes and a septic screen. Laboratory results revealed a TSH level of < 0.01 mIU/L and T4 level of 10.0 pmol/L indicative of central hypothyroidism. The rest of the biochemistry was within a normal range, with a negative septic workup. Imaging was requested, and an uncontrasted CT brain scan revealed a poorly defined cystic lesion in the suprasellar region of the brain, suggestive of central hypothyroidism. Results from a lumbar puncture were unremarkable, aside from raised protein levels of 2.89 g/L. Unfortunately, the patient demised prior to an MRI scan being performed.

The question was then posed whether thyroid dysfunction is an identifiable risk factor for the development of cutaneous squamous cell carcinoma (SCC). The following discussion aims to explore this.

Discussion

There are multiple risk factors strongly associated with the development of SCC. The most well-known are the phenotypic characteristics: red hair, fair skin (with long exposure to UV radiation), suntanning, HIV, as well as other genetic or immune and environmental risk factors.[1,2] In the African population, high levels of melanin serve as a protective factor against UV rays.[3] However, SCC is still a frequently diagnosed dermatological malignancy, developing in sun-protected areas of the body such as the lower leg, particularly in sites of chronic ulceration and previous burns that are not related to sunburns.[2,4] The development of SCC occurs by malignant transformation of epidermal skin cells. UV rays damage DNA in cells, leading to genetic defects with ongoing replication.[5]

Primary hyperthyroidism is defined as low levels of TSH and elevated levels of 3, 5, 3'-triiodo-L-thyronine (T3) and T4, while hypothyroidism is diagnosed when the TSH is elevated and the T4 is low.[6] Central hypothyroidism is characterised by low levels of both TSH and T4.[7] Clinical manifestations on the target organ in both hyper- and hypothyroidism are as a result of T4 levels. The cutaneous manifestations of hypo- and hyperthyroidism are mainly attributed to the dysregulation of epidermal homeostasis resulting in either dry and course skin with myxoedema or smooth skin with thyroid acropachy, respectively.[8]

Thyroid dysregulation has long been implicated in the pathogenesis of cancer. The link between thyroid dysregulation and cancer involves complex interactions that influence both cancer risk and progression. There is more evidence supporting

Table I: Effect of thyroid enzymes on T4 and their link to squamous cell carcinoma[17]

Thyroid enzyme	Effect on T4	Effect on SCC
Increased expression of D2	Activates conversion of T4 to T3	Tumour growth and increase in size (tumour size) Correlates with tumour grade and increased rate of post-surgical relapse
Increased expression of D3	Inactivates T4 or T3	Tumour initiation (number of tumours)

the role of hyperthyroidism in the pathogenesis of cancers, with hypothyroidism having an inhibitory effect in some cancers.[9] This case report postulates that hypothyroidism is implicated in the development of SCC.

A study conducted by Ahadiat et al., 2018 highlighted a prominent link between hypothyroidism and the development of cutaneous SCC as seen in this case report. The retrospective review showed that 31% of patients with SCC were previously diagnosed with hypothyroidism.[10] It was concluded that individuals with SCC are more likely to have a history of hypothyroidism compared to the general population.

Lobl et al., 2022 conducted a multi-institutional, case-controlled study of 65 cutaneous SCCs with known lymph node metastasis matched with 195 cutaneous SCCs without lymph node metastasis. Hypothyroidism was identified as a key risk factor for SCC in lymph node metastasis (OR 2.7 CI 95% 1.04–7. 0).[11]

Hypothyroidism has been associated with several types of cancer, including thyroid cancer, colon cancer, breast cancer, and hepatocellular carcinoma. Studies have indicated connections between hypothyroidism and these cancers, though the precise nature of these relationships is still being explored.[9,10,12-16] Currently, there is limited evidence linking hypothyroidism to any type of skin cancer, specifically SCC.

Despite extensive research on hypothyroidism, there is a need for larger studies to establish a conclusive connection between hypothyroidism and any type of skin cancer, including SCC. However, given the significant impact hypothyroidism has on the skin, exploring a potential link between hypothyroidism and skin cancer is a logical area for further investigation.[10]

Possible mechanisms to explain the pathogenesis of hypothyroidism-induced cancers involve the expression levels of the thyroid enzymes. Thyroid enzymes iodothyronine deiodinases type 1 and 2 (D1 and D2) have a role in activating thyroid hormone T4 to its more active form, T3, and deiodinsases D3 and D4 are responsible for inactivating it, thus maintaining homeostasis.[17]

A study conducted by Miro et al., 2019 showed the correlation of D2 and D3 to tumour behaviour by introducing SCC into mouse subjects. Tumour behaviour was then monitored by depleting the mice of the respective enzymes. The main findings of the study are summarised in Table I which highlight the link between thyroid enzymes, T4 and their effects on SCC.[17]

This supports the hypothesis that thyroid hormone (activated by D2 – cited as a "metastasis promoter") appears to be central in the progression of tumours to the metastatic stage. Based on this research, the previously accepted linear model of tumour progression is challenged, particularly regarding SCC. Thyroid hormone plays a crucial role in promoting cell migration and accelerating metastasis. This conclusion is further supported by observations that reducing thyroid hormone accelerates tumour formation but decreases invasiveness.[17]

The aforementioned examples explore the way in which thyroid hormone levels affect tumour behaviour. Another earlier publication by Ellerhorst et al., 2006 explored the role of TSH in melanoma. Findings showed that TSH receptors (TSH-R) on melanoma cells are functional and hypothesised that TSH could be a growth factor for melanoma cells. It is postulated that in SCC, hypothyroidism may act in a similar manner due to the patients having a certain degree of immune dysfunction.

While pathogeneses are well described in other cancers, the exact mechanisms in skin cancer, specifically SCC, are not well understood.[9] There is a lack of sufficient case studies and population studies to indicate the link between SCC and hypothyroidism and, therefore, the statistical power is not strong enough to conclusively establish causality. Therefore, more studies are required to strengthen the body of evidence linking hypothyroidism to SCC.

Conclusion

This case study has highlighted the link between hypothyroidism and SCC and emphasises the multifaceted role of thyroid hormones in cancer development. This report underscores the value of thyroid function testing in patients with newly discovered malignant tumours, specifically SCC, with special consideration in people of colour, where SCC is not often expected. Current evidence in literature is not sufficient to prove causality and requires further investigation, particularly in people of colour. The mechanisms discussed are part of ongoing research and continue to contribute to the understanding of cancer pathogenesis.

Conflict of interest

Authors have no conflict of interest to declare.

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