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Anaplastic Transformation of Differentiated Papillary Thyroid Carcinoma Presenting as Cauda Equina Syndrome

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Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Patient: Female, 67-year-old
Final Diagnosis: Thyroid cancer
Symptoms: Weakness of lower limbs
Medication: —
Clinical Procedure: —
Specialty: Oncology





Objective: Unusual clinical course
Background: Papillary thyroid carcinoma is usually an indolent disease, with an almost 80% 5-year survival rate for metastatic disease. Conversely, anaplastic thyroid cancer is much more aggressive, with median overall survival rates of 4 months.

Case Report: A 67-year-old woman presented with metastatic papillary thyroid cancer with bone metastasis, including an unstable L4 pathological fracture. Initially, she underwent lumbar stabilization surgery, followed by high-dose palliative radiotherapy to the lumbar spine. Subsequently, a total thyroidectomy was performed, followed by an ablative dose of radioiodine and supraphysiological doses of levothyroxine to achieve TSH suppression to less than 0.1 mU/L. The treatment dose of radioiodine was administered 4 times at 6-month intervals. The treatment was well tolerated, with a dramatic thyroglobulin response, and the disease remained radioiodine-sensitive. Prior to a fifth planned dose of radioiodine, our patient presented with cauda equina syndrome and underwent urgent decompressive surgery. Further oncological treatment was planned; however, she deteriorated rapidly following surgery, and repeat imaging showed progressive disease at the surgical site. Histopathology from the lumbar decompression revealed anaplastic thyroid cancer. Our patient died 5 weeks after surgery.

Conclusions: This is the first published case of transformation from papillary to anaplastic thyroid cancer presenting as cauda equina compression. Transformation from papillary to anaplastic thyroid cancer has been previously described in the literature; however, it is rarely present distant from the neck, and has an aggressive course. Malignant transformation should be considered in cases of differentiated thyroid cancer that do not fit the previous disease trajectory.

Keywords: Cauda Equina Syndrome • Thyroid Cancer, Papillary • Thyroid Neoplasms

Full-text PDF: <https://www.amjcaserep.com/abstract/index/idArt/932002>

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Background

Papillary thyroid carcinoma is usually an indolent disease and has a 5-year survival rate of 78% for metastatic cases [1]. Distant metastases occur in approximately 10% of patients with differentiated thyroid carcinoma and are found at presentation in half of these cases. Conversely, anaplastic thyroid carcinoma behaves in an aggressive manner, typically presenting at an advanced stage, with a median overall survival of 4 months [2].

Transformation from a papillary to an anaplastic thyroid carcinoma has been described in the literature, both local to the thyroid [3,4] and at a variety of distant sites [5-8]. Distant transformation, however, remains rare. We present a case of a radioiodine-sensitive papillary thyroid carcinoma transforming to an anaplastic thyroid carcinoma, presenting as a cauda equina compression.

Case Report

A 67-year old woman presented with a 1-year history of back pain. Magnetic resonance imaging (MRI) showed an unstable fourth lumbar vertebral (L4) lesion with an associated pathological fracture (Figure 1A). A fluorodeoxyglucose (FDG)-positron emission tomography (PET) scan revealed focal increased activity in the right lobe of the thyroid, a lumbar spinal mass,

and an FDG-avid left axillary lymph node. An ultrasound scan of the axilla and thyroid revealed several thyroid nodules (all U2 in appearance) and benign axillary lymph nodes. The patient underwent an L4 corpectomy with L3 to L5 screw fixation. The histopathology from the L4 lesion was consistent with a diagnosis of a follicular variant of papillary thyroid carcinoma; immunohistochemistry was positive for pan-cytokeratin, CK7, thyroglobulin, and TTF-1. No poorly-differentiated component was identified (Figure 2).

Based on the spinal pathology results, a total thyroidectomy and central neck dissection were performed. A 13-mm unifocal papillary carcinoma (unencapsulated follicular variant) in the left thyroid lobe was identified, which was narrowly but completely excised with no associated lymphovascular invasion. No poorly-differentiated or anaplastic components were present. The final staging was pT1bNxM1(bone) (TNM8) and the patient was started on supraphysiological doses of levothyroxine to suppress the TSH to less than 0.1 mU/L.

An ablative dose of radioiodine (3 GBq) was administered with uptake on the post-ablation I^{131} scan seen in the thyroid bed, ribs, right ilium, and sacroiliac joints and fourth lumbar vertebrae region. An initial stimulated thyroglobulin value was recorded as 207 320 ug/L (unstimulated, 12 479 ug/L). Following this, a course of external beam radiotherapy was delivered to the lumbar-sacral spine: 30 Gy in 10 fractions over 2 weeks. Four consecutive treatment doses of I^{131} (5.5

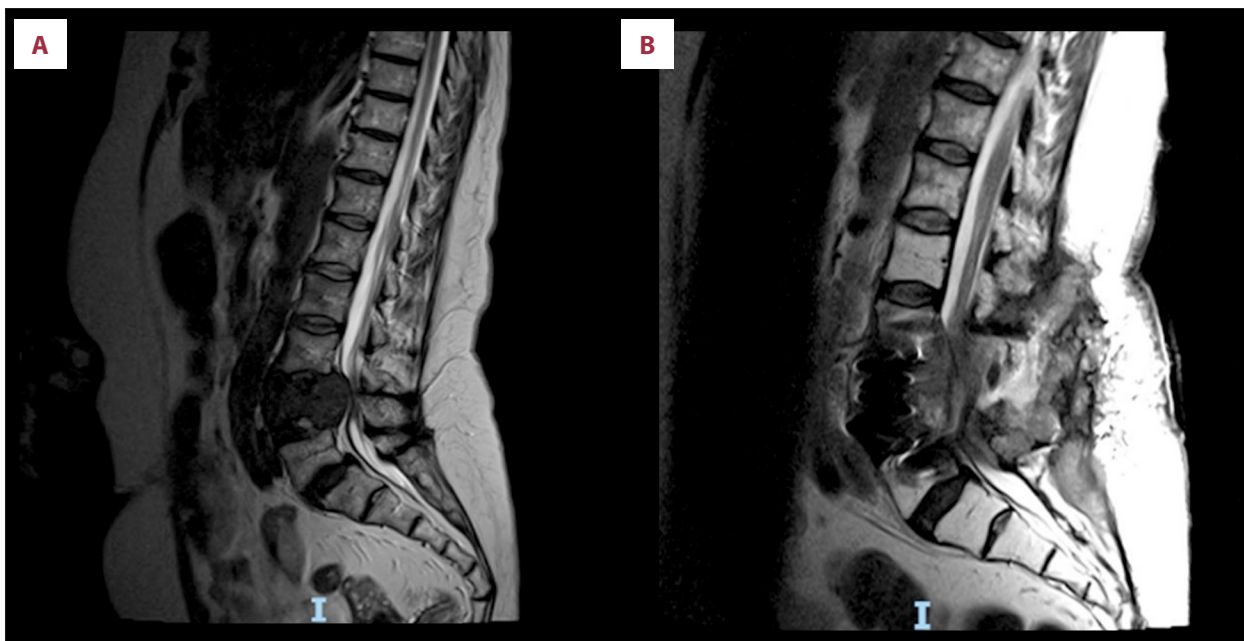


Figure 1. (A) Sagittal T2-weighted magnetic resonance imaging (MRI) of lumbar-sacral spine showing cauda equina compression at L4 level at first presentation of differentiated thyroid cancer. (B) Sagittal T2-weighted MRI of lumbar spine showing progressive disease, complex abscess formation, and cauda equina compression at L4 level at point of anaplastic thyroid cancer transformation.

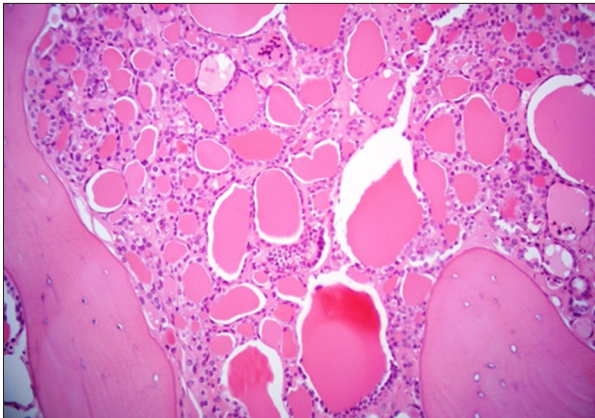


Figure 2. Hematoxylin- and eosin-stained biopsy specimen from L4 vertebra (2016) showing infiltration by metastatic well-differentiated thyroid carcinoma, ×200 magnification.

GBq) were subsequently delivered at 6-month intervals. The post-therapy scans demonstrated persistent but reduced iodine uptake within the L4 vertebrae and faint uptake within the right ilium and sacroiliac joint, with no abnormalities seen elsewhere on the associated single-photon emission computed tomography scan, and stimulated thyroglobulin levels falling to 226 ug/L (unstimulated thyroglobulin, 93 ug/L) at the time of the last therapeutic dose. The patient remained well and free of pain, with an unstimulated thyroglobulin recorded at 69 ug/L at the most recent follow-up. Radioiodine doses had been well tolerated, but with some mild myelosuppression (neutrophils of $1.27 \times 10^9/L$). Therefore, a further treatment dose of I^{131} (5.5 GBq) was scheduled for when the bone marrow counts had recovered.

Two months prior to the planned admission for radioiodine, the patient presented as an emergency to her local hospital with worsening back pain, urinary retention, and lower-limb weakness. Cauda equina compression at L3 to L5 was confirmed, and an emergency lumbar decompression was performed. The patient's recovery and rehabilitation after surgery were slow, with her experiencing general functional decline and failure to improve with therapy. Repeat imaging 2 weeks after surgery revealed rapid progressive disease, with a complex abscess formation in the lumbar spine at the site of surgery, causing recurrent tumor compression of the cauda equina (**Figure 1B**), together with further multifocal disease in the subcutaneous tissues, with the tumor seen emerging from the surgical wound and infiltration of both psoas muscles, resulting in hydronephrosis and multiple lung metastases. Histopathology examination from the lumbar spine showed a poorly-differentiated malignant tumor (**Figure 3A**). Immunohistochemical staining showed the tumor cells were strongly positive for Pax8 (**Figure 3B**), a pan-cytokeratin stain (AE1/AE3), and CK7 (**Figure 3C**). There was also weak staining for GATA-3 and no

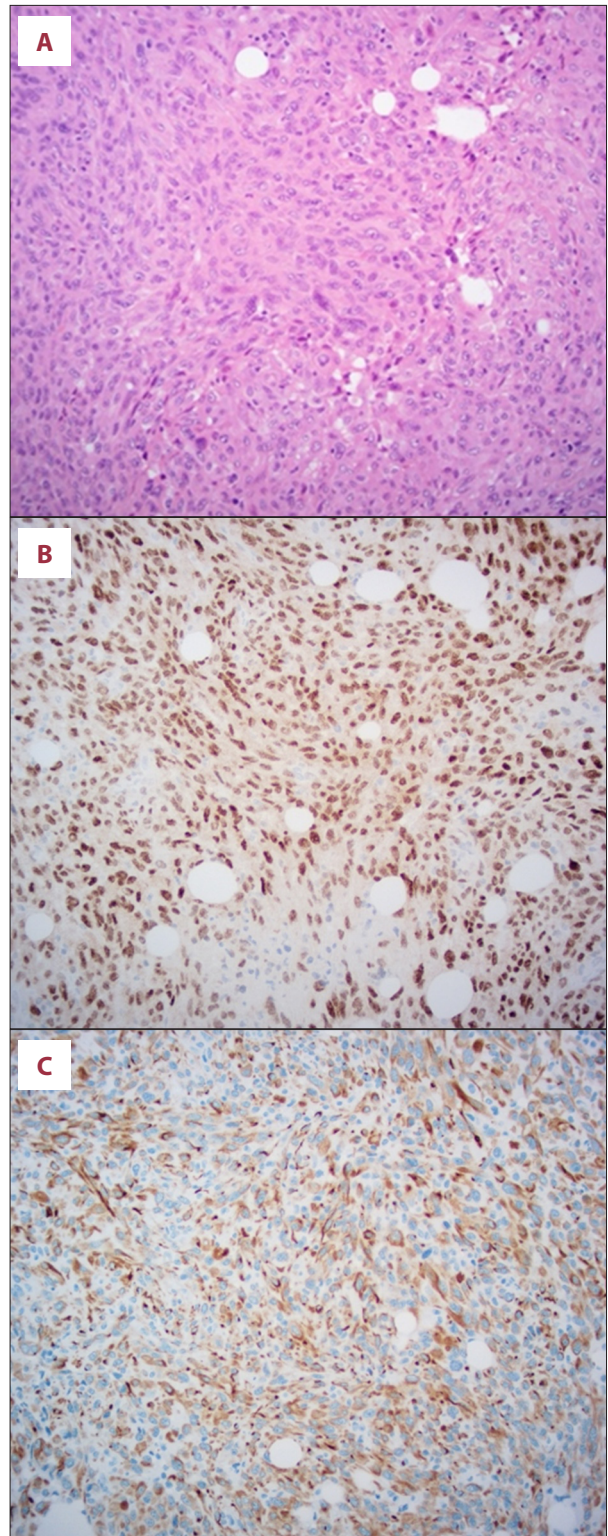


Figure 3. (A) Hematoxylin- and eosin-stained biopsy specimen from L4 vertebra (2020) showing a high-grade malignant tumor, ×200 magnification. Immunohistochemical staining for (B) Pax8 and (C) CK7.

staining for CK20, CK5, p63, TTF-1, SMA, MyoD1, calcitonin, S100, MelanA, HMB45, CD45, C125, and WT-1. The serum unstimulated thyroglobulin level was 47.4 ug/L. In view of the patient's rapid clinical deterioration, findings on imaging, histological appearance, and immunophenotype, the features were felt to be consistent with a diagnosis of anaplastic carcinoma of the thyroid. The oncology and palliative care teams were involved, but, unfortunately, the patient was not fit for further oncological treatment and died in the hospital 5 weeks after surgery. The patient's overall survival from the time of initial papillary thyroid cancer diagnosis was 3 years 3 months.

Discussion

Local transformation from differentiated papillary thyroid cancer to anaplastic cancer within the thyroid gland is reasonably well reported in the literature [3]. Transformation in the cervical lymph nodes has also been described, and good outcomes for these patients following neck dissection have been reported [9].

Conversely, distant-site transformation has been less widely reported and only described in case reports at a number of sites, including the retroperitoneum [8], lungs [7], pleura [10], mandible [6], and breast [11]. In all of these cases, the cancer behaved aggressively with associated rapid clinical deterioration. The natural history from diagnosis of differentiated thyroid cancer to anaplastic transformation in these reports ranged from 7 to 30 years. This contrasts with our patient's case, in which the time was shorter, at only 3 years, highlighting the unpredictable and individual nature of this disease process.

BRAF, p53, and TERT promotor mutations, among others, have been identified as important factors in the development of anaplastic carcinoma that arise from existing well-differentiated thyroid tumors such as papillary and follicular carcinoma. These mutations are thought to occur prior to transformation, as have been shown in both papillary and anaplastic components, and to indicate a worse prognosis in the differentiated tumor, even in cases where anaplastic transformation did not occur [12,13]. Other studies have implicated 8 significantly altered markers between the 2 tumor types: upregulation of p53, MIB-1, and topoisomerase II- α and downregulation of thyroglobulin, E-cadherin, B-catenin, Bcl-2, and VEGF in the anaplastic tumor, compared with the differentiated tumor [14]. However, none of these mutations were tested in our patient in either tumor sample. Radioiodine (131 I) has additionally been implicated as a potential causative factor in the development of p53 mutations in differentiated thyroid cancer [15].

There is also evidence suggesting early evolutionary divergence between the 2 tumor types, as it has been shown that many of the mutations identified in the respective tissue types do not overlap [16]. This challenges the more widely recognized hypothesis of transformation from a differentiated tumor to an undifferentiated one and suggests that perhaps the 2 tumors evolve separately. Alternatively, it may be that both hypotheses hold true, and that in patients with coexistent differentiated and anaplastic thyroid tumors, some have evolved directly from the differentiated tumor, while others are part of a distinct evolutionary process and have simply occurred simultaneously in the same patient. The fact that our patient had biopsy-confirmed disease of both cancer types from the same site distant to the thyroid (L4 vertebra) does, however, seem to support a process of transformation in our patient.

The prognosis for anaplastic thyroid carcinomas is improving as newer targeted treatment options become available. Good response rates (overall response rates of 69%), have been demonstrated in patients with tumors containing a BRAF V600E mutation who received dabrafenib and trametinib [17], demonstrating the importance of early molecular testing in de novo anaplastic tumors, but also in transformed differentiated tumors.

Conclusions

This is the first reported case of transformation from a papillary to an anaplastic thyroid carcinoma presenting as a cauda equina compression. Furthermore, many of the previously reported cases in the literature were diagnosed only at autopsy, whereas our patient was still alive at the time of diagnosis. This enabled essential communication with the patient and family, particularly involving discussions about prognosis and benefits of further treatment. This case highlights that malignant transformation of papillary thyroid carcinoma should be considered in the differential diagnosis when the current presentation does not reflect the previous disease trajectory. Further molecular profiling [18] may offer information on prognosis [19] and identify opportunities for newer targeted therapies [20] and perhaps should be considered early in a patient's management course. However, our case also highlights the rapidity with which malignant transformation of a differentiated thyroid cancer can occur and prove fatal.

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