

## Renal Involvement in Cases of Spindle Epithelial Tumor with Thymus-Like Differentiation: A Case Report and Review of the Literature

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### ABSTRACT

**Background:** Spindle epithelial tumor with thymus-like differentiation (SETTLE) is a very rare neoplasm of the thyroid first described by Chan and Rosai in 1991. Renal involvement usually occurs as part of a disseminated metastatic picture. SETTLE is believed to arise from branchial pouch or thymic remnants and shows primitive thymic differentiation.

**Presentation:** A 41-year-old male presented with a thyroid mass in 2005. The patient underwent a total thyroidectomy followed by radiation therapy. Pathology concluded papillary thyroid cancer. In 2011, the patient was admitted with worsening cough. CT showed lung involvement, multiple mediastinal lymph nodes, and a left renal mass. A biopsy established the diagnosis of SETTLE. Four cycles of platinum chemotherapy were given. In 2014, the patient was referred to Urology with progressive flank pain and hematuria. CT showed a progression of the renal mass, and results of an U/S guided biopsy of the kidney were consistent with SETTLE. An elective radical nephrectomy was performed in late 2016 to relieve symptoms. The patient is currently being followed as an outpatient.

**Conclusion:** Due to the rare nature of SETTLE, algorithms for the diagnosis, treatment, and outcomes are not established. Although SETTLE presents as a low-grade malignancy, this case, as well as other reported cases with a long follow-up duration, suggested that it can metastasize many years after initial diagnosis. More data is needed to elucidate the risk and prognosis of renal metastasis in SETTLE.

**Keywords:** SETTLE, spindle epithelial tumor with thymus-like differentiation.

### INTRODUCTION

Spindle Epithelial Tumor with Thymus-Like Differentiation (SETTLE) is a remarkably rare tumor of the thyroid gland – less than 50 clinical cases - that was first observed and described by Chan and Rosai in 1991<sup>(1)</sup>. SETTLE is believed to arise from branchial pouch or thymic remnants, and it displays primitive thymic differentiation<sup>(2)</sup>. It is mostly a disease of the younger population (an average of 18 years old) and can lead to the development of delayed blood-borne diseases and metastases to lymph nodes, lungs, pancreas, and kidneys<sup>(3)</sup>. Kidney involvement is usually part of a disseminated metastatic picture. Initial diagnosis of this disease is challenging due to the lack of specific signs and symptoms.

Histologically, SETTLE's predominant feature involves a low-grade biphasic tumor with metastatic potential that is characterized by low mitotic activity, rare focal necrosis and with usually indolent growth. It is characterized by fascicles of spindle cells intermingled with tubulopapillary structures<sup>(4)</sup>.

#### Research aims and objectives

Our first objective is to perform a systematic literature review on the topic of SETTLE, emphasizing on case reports available in the literature. We especially want to distinguish and

register case studies that report renal involvement, thus registering the prevalence of such implication as a result of this disease. It is also our aim to pinpoint any drawbacks and limitations observed in these case reports such as lack of adequate follow-up time, or even loss of follow-up.

Our second objective is to present our experience with our case, which was referred to Urology with progressive flank pain and haematuria. Our case is a follow up on a case reported by Recondo *et al.*<sup>(8)</sup>. We specifically want to outline how alternative management earlier in the course of the disease could have resulted in a different outcome.

#### Systematic review of the literature

Systematic literature reviews are, practically, key parameters of public health, nursing, and evidence-based healthcare because they can provide results and conclusions that rely on – and verify - a previously formulated question.

### METHODOLOGY

As defined in PRISMA guidelines, there is a need in applying specific eligibility criteria that will guide researcher's decision on study inclusion into this analysis. A retrieved article/source will only be eligible for inclusion if the respective source reports either primary or secondary research and follows a valid research methodology such as RCT, cohort

studies, meta-analysis, systematic literature reviews. Sources will only be eligible for inclusion if the respective source reports data that are directly referring to the previously defined aims and objectives of this project by specifically including potential renal implications. We only considered articles published in English and available as full text. A retrieved article/source will not be eligible for inclusion in cases where the reported data do not have distinct and precise scientific validity, or violates aforementioned inclusion criteria

### **Search Strategy**

A thorough search was performed in various electronic databases such as PubMed, Cochrane Library, EMBASE, BIOSIS Previews, Science Direct, PLOS, etc. It is highly critical to define appropriate text and keywords, determine potential synonyms for text, and also to consider various spellings. In our case, keywords included: 'SETTLE, Spindle epithelial tumor with thymus-like differentiation, kidney metastases, tumor (or 'tumour') of the thyroid gland, neck mass.' It should be mentioned that it is easy to find several articles that are directly or indirectly relate to the issue under investigation; however, the hard part is to distinguish which study is of real practical use and can indeed contribute to the findings that this systematic literature review wants to verify and exhibit. Therefore, details such as the journal on which it was published, the year of publication, the authors, the content of the article, are of equal and more advanced importance.

### **Study Selection Process**

The study selection process is essentially based on distinct steps<sup>(6)</sup>. First of all, it is essential to apply our inclusion and exclusion criteria, a fact that will, in turn, ensure that the resulting research studies will be classified accordingly and correctly. Consequently, we need to eliminate and exclude all research studies that do not meet our inclusion

criteria. Abstracts can be misleading, especially when it comes to the validity of research studies, and hence this is why this systematic literature review will not take into consideration research studies that cannot be fully retrieved from the respective databases (third step). This will unavoidably limit the number of included articles, it is nevertheless essential, for maintaining a highly accurate degree of incoming articles and publications that specifically answer our predetermined objectives. The fourth and the fifth step both include identification (and subsequent evaluation) of the quality of the incoming resources. It is highly beneficial to exclude (and of course include) studies that meet a minimum threshold of quality. Therefore, included articles need to lack any bias and meet no exclusion criteria. Keep in mind that the higher the impact factor of a specific magazine or publishing house the more consistent, accurate, and well-defined are the respective results and conclusions. The last step of the selection process allows us to include the remaining studies in our systematic literature review, and thus proceed with the interpretation and analysis of the respective data.

**The study was done after approval of ethical board of King Abdulaziz university.**

### **Search Results**

In total, after searching aforementioned databases and applying our criteria, 32 research studies and clinical cases were identified<sup>(7-38)</sup>. Table I shows specific cases where renal implications were observed, including any potential drawbacks of the respective research designs (usually involving a very short follow-up period). Keep in mind, that SETTLE demonstrates prominent delayed metastases to lymph nodes, lungs or kidneys. Hence follow-up period must be long enough to include and register such potential outcomes.

**Table 1:** Cases that showed renal involvement

<i>Number of Studies</i>	<i>Principal objectives included</i>	<i>Renal implications</i>	<i>Clinical Course of the disease/ Treatment</i>	<i>Comments/Limitations</i>
3-	YES	YES	Metastases to lungs.	Follow-up period of 8 years (the only study having such long follow-up period)
			Initial treatment: Lobectomy	
			Followed by chemotherapy	
7-	YES	YES (Metastasis to right kidney)	Initial treatment: Lobectomy	Follow-up period 2 years
			Followed by chemotherapy and nephrectomy	
8-	YES	YES (Metastases to lungs and kidneys)	Total thyroidectomy followed by chemotherapy	Very short follow-up period.



*Figure 1: Gross pathology of kidney lesion*

### CASE STUDY

Our patient is a 41-year-old male presented with a thyroid mass in 2005. The patient underwent a total thyroidectomy followed by radiation therapy. Pathology concluded papillary thyroid cancer. In 2011, the patient was admitted with worsening cough. A CT scan showed lung involvement. In late 2012, whole body imaging showed metastatic disease to the neck and left kidney. A biopsy established the diagnosis of SETTLE. Four cycles of platinum chemotherapy were given.

In 2014, the patient was referred to Urology with progressive flank pain and hematuria. CT showed a progression of the renal mass, and results of an ultrasound guided biopsy of the kidney were consistent with SETTLE. An elective radical nephrectomy was performed in mid 2016 to relieve symptoms. According to the histopathology report of the tumor, the tumor size was 17 cm in maximum dimension. Tumor necrosis involved around 15% of the tumor. Also there was tumor invasion to the renal sinus and into perirenal fat. Extensive lymphovascular invasion was noted.

In late 2016, a CT study was done and showed interval increase in the size of the enhancing soft tissue density at the bed of the left nephrectomy consistent with interval increase residual / recurrence. Significant interval increase in the lung and liver metastasis in keeping with the interval progression of disease was seen. 6 cycles of chemotherapy were started afterwards. The patient is currently being followed as an outpatient and is undergoing palliative care and radiotherapy for

progressive pain in the left flank with neuropathic features.

### DISCUSSION

Although SETTLE was first described by Chan and Rosai in 1991, there is substantial evidence of this disease in the literature that dates back to 1976 and 1979<sup>(20,22)</sup>. Of course, the description of SETTLE was that of ‘an unknown disease in the neck region’. A common shortcoming shared by most studies we included in our review was short follow up period – in fact, in some cases, there was no follow-up – and the average follow-up time was two years. The site where the tumor was observed was at the neck region (right thyroid mass, thyromegaly, neck mass) and the initial means of treatment included lobectomy, total thyroidectomy, nodule excision, usually accompanied by chemotherapy (11 cases).

Several studies have identified metastases to lymph nodes<sup>(1, 3)</sup>, lungs<sup>(5, 12, 14, 16, 20, 22)</sup>, vertebrae<sup>(7)</sup>, and kidneys<sup>(3, 7-8)</sup>. Metastases was observed as late as 11 years following the identification of the tumor, thus demonstrating the importance of an extensive follow up period<sup>(7)</sup>. More specifically, rates of metastasis were approximately 20%; however, these incidence rates were found highly increased in case of long-term (more than 4-5 years) follow-up periods. It should be mentioned that there was only one study that reported patient death<sup>(3)</sup>: one of the very few studies that included a substantial and extensive follow-up period (8 years). However, the association between SETTLE and high mortality rates is by no means

documented or established. This comes to demonstrate the indolent course of the tumor

## CONCLUSION

Although only three cases reported renal metastasis, it is essential to consider renal implications early in the course of the disease. This is especially critical considering the poor outcomes associated with renal involvement - one case being dead and another undergoing a radical nephrectomy. More aggressive management early in the course of the disease could be akey to prevent such outcomes.

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