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Spindle cell carcinoma of the lower lip: A case report and review of the literature

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BK Bunn[1], P Gwengu[2], D Nelwamondo[3]

ABSTRACT

Background

To document the lip as an unusual site of clinical presentation of spindle cell carcinoma and to conduct a review of the literature.

Methods

A 66-year-old male patient presented with an ulcerated lesion of the lower lip. Morphological examination and immunohistochemical profiling of the lesion were performed.

Results

Histopathological examination showed a high-grade spindle cell neoplasm. Pleomorphic fusiform cells with cytological and nuclear atypia were predominant together with conspicuous perineural infiltration. A small focus of overlying stratified squamous parakeratinising epithelium was identified in a section of the lesion. Co-expression of cytokeratin and mesenchymal markers confirms the epithelial-mesenchymal transition which is inherent to this lesion.

Conclusion

Spindle cell carcinoma (sarcomatoid carcinoma) is a rare variant of squamous cell carcinoma with an infrequent occurrence on the lower lip. The objective in reporting this case is to raise the clinicopathological awareness of this unconventional variant of squamous cell carcinoma to expedite diagnostic and therapeutic intervention.

Statement of clinical relevance

The documentation of a rare form of oral squamous cell carcinoma at an unusual site allows for expeditious diagnostic and therapeutic intervention.

Authors' information

1. Dr Belinda Kathleen Bunn, BDS, FCPath (SA)Oral Path, MDent (Oral Path), Department of Operative Dentistry, Oral and Dental Hospital, Sefako Makgatho Health Sciences University, South Africa. ORCID: 0000-0001-5699-4997
2. Dr Pumela Gwengu, DipOH, BDS, MPH, MDent (Com Dent), Department of Operative Dentistry, Oral and Dental Hospital, Sefako Makgatho Health Sciences University, South Africa
3. Dr Dakalo Nelwamondo, BDS, Department of Maxillofacial and Oral Surgery, Sefako Makgatho Health Sciences University, South Africa

Corresponding author

Name: Dr Belinda Bunn
Email: belindabunn@gmail.com
Tel: +27 82 708 5868

Author's contribution

1. Principal researcher – writing, microscopic analysis (40%)
2. Co-authors – editing, contribution to concept, clinical contribution of patient information (30% each)

Keywords

Spindle cell carcinoma, squamous cell carcinoma, sarcomatoid carcinoma, epithelial-mesenchymal transition

Conflict of interest

No conflict of interest declared

INTRODUCTION

Spindle cell carcinoma (SpCC) represents a rare variant of squamous cell carcinoma (SCC), an epithelial malignancy which has a predominant mesenchymal morphology.[1,2] The diagnosis of SpCC is frequently problematic particularly when there is no microscopic evidence of origin from the overlying epithelium. SpCC thus presents with great diversity within each individual neoplasm as well as variation between neoplasms, which adds to the complexity of diagnosing neoplastic spindle cell lesions at this site.[1]

Spindle cell carcinoma is also variably termed sarcomatoid carcinoma which reflects its true epithelial nature using the term "carcinoma" as well as the fact that both at a morphological and molecular level, the neoplastic cells undergo epithelial-mesenchymal transition (EMT) which provides the sarcomatoid component to its name.[3,4] As a variant of squamous cell carcinoma, it exhibits biological aggressivity and is often associated with an overall poor prognostic outcome.[2,4-9] This is in part a result of the prominent EMT which increases the probability of early/nodal metastases thus increasing the clinical stage at presentation and accounting for the greater incidence of recurrence associated with this form of SCC.[2,7,8,10,11] SpCC is most frequently identified in the head and neck within the larynx, trachea, tongue and maxillary sinuses.[2,5,7,12] Other cases involving the oral cavity are rare with documentation at sites including the lower lip, buccal mucosa and attached gingiva.[2,6,8,13-15] SpCC occurring primarily on the lip presents more often as an ulcerated, endophytic lesion and often has regional lymph node metastases at the time of clinical presentation. This is prognostically significant and confirms the need for increased awareness of SpCC at this site to ensure the accurate diagnosis and implementation of the appropriate management.

CASE REPORT

A 66-year-old male patient presented with a painful ulcer of the lower lip which had been present for nine months. The patient had reported sudden rapid pre-operative growth. Clinical examination showed an area of ulceration with rolled borders measuring 20x40mm in size (Figure 1). In addition, the patient was known to be RVD-reactive with a history of tobacco use and alcohol consumption. There was clinical evidence of bilateral submandibular lymphadenopathy. The clinical impression was that of squamous cell carcinoma. The sections of tissue submitted for histopathological examination confirmed the presence of a malignant predominantly spindled neoplasm which was noted to arise within the overlying oral mucosa of the vermillion border. The patient was unfortunately lost to follow-up which prevented definitive surgical management.

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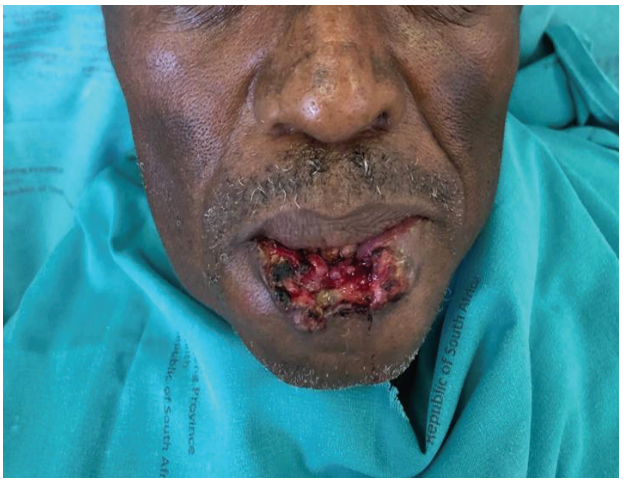

Figure 1: Clinical presentation of an ulcerated lesion on the lower lip of a 66-year-old male patient which had been present for nine months.

METHODS

The surgical incision specimen was received in a 10% formaldehyde solution followed by macroscopic examination. The tissue was embedded in paraffin, processed and stained routinely with hematoxylin and eosin. Following histomorphological assessment, immunohistochemical staining was performed on four micrometer sections which were first deparaffinised and hydrated followed by antigen retrieval. The antibodies used in this case are listed and summarised in Table I. Positive and negative controls were used for the verification of the staining in each case.

RESULTS

Macroscopic examination

Two separate specimens were submitted as incisional biopsies of the lesional tissue. Specimen 1 comprised two soft tissue fragments, the larger measuring 13x5x5mm and the smaller measuring 11x6x3mm. The first specimen was labelled "left lower lip" and appeared to be surfaced by mucosa. The second specimen was labelled "right lower lip" and comprised a portion of soft tissue measuring 11x6x4mm.

Microscopic examination

Both specimens showed similar histological features and are therefore described together. Sections show portions of soft tissue surfaced on one aspect by stratified squamous non-keratinising epithelium. There is focal evidence of ulceration where an adherent layer of inflammatory crust material is present. Arising within the surface epithelium is a malignant neoplasm. The invasive tumour cells are predominantly fusiform with marked nuclear and cytological atypia and pleomorphism. Occasional scattered foci containing plumper, more epithelioid cells are observed (Figure 2A). Multifocal areas of perineural infiltration are evident.

Expression of the cytokeratin marker AE1/AE3 is positive in both the overlying epithelium as well as within the underlying neoplastic tumour cells (Figure 2B). A second marker of epithelial morphology is p63 which shows diffuse, strong nuclear positivity within the neoplastic cells (Figure 2C). Furthermore, the neoplastic tumour cells show divergent differentiation through the co-expression of Vimentin, a marker of mesenchymal origin (Figure 2D).

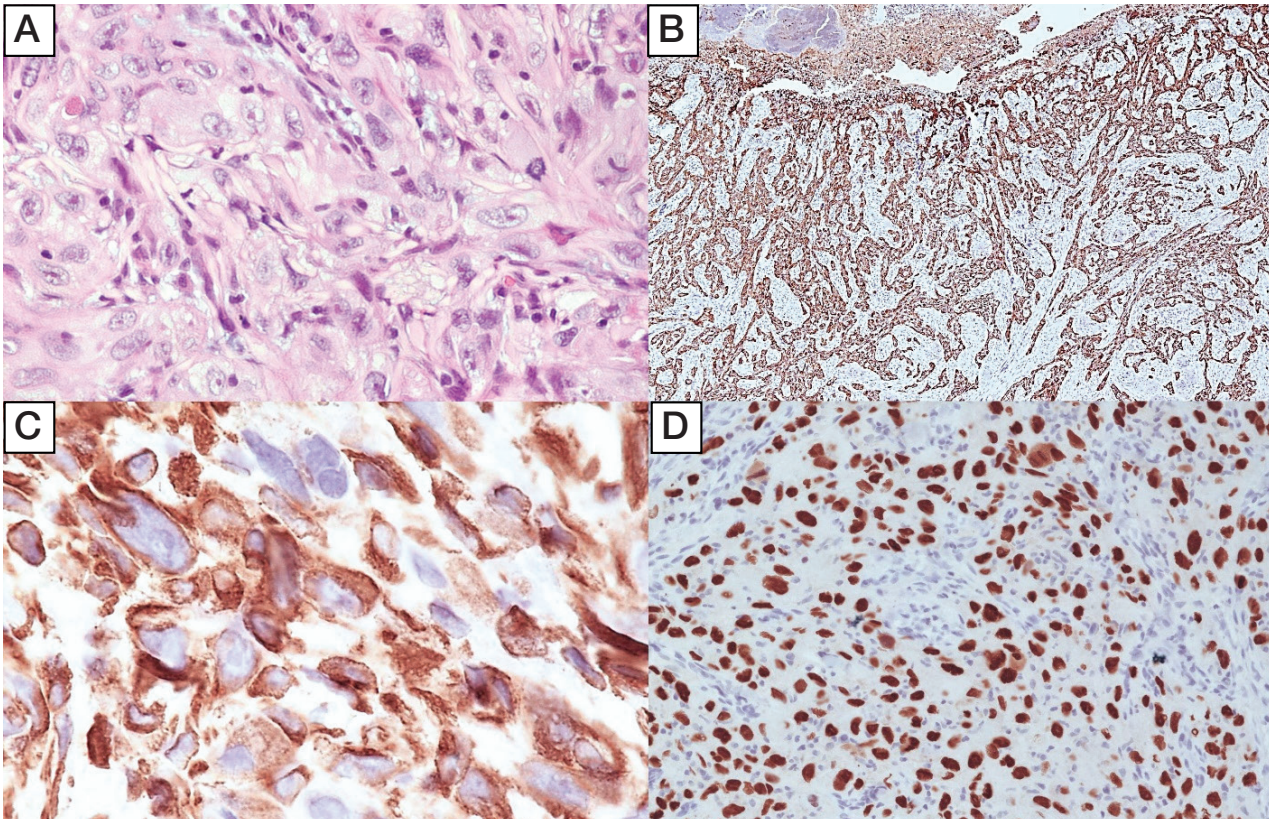

Figure 2A: High-grade epithelioid and fusiform tumour cells with marked cytological pleomorphism and mitotic atypia (Hematoxylin-eosin stain, original magnification x100). **Figure 2B:** Cytokeratin staining of the neoplastic cells is strongly and diffusely positive. The surface ulceration is highlighted here while the stain demonstrates strands, cords and single cell invasion by the tumour cells (Immunohistochemical staining with AE1/AE3, original magnification x200). **Figure 2C:** Co-expression of Vimentin with AE1/AE3 shows divergent lineage of the tumour cells due to epithelial-mesenchymal transition (Immunohistochemical staining for Vimentin, original magnification x200). **Figure 2D:** p63 nuclear positivity is diffusely expressed within the tumour cells (Immunohistochemical staining with p63, original magnification x200).

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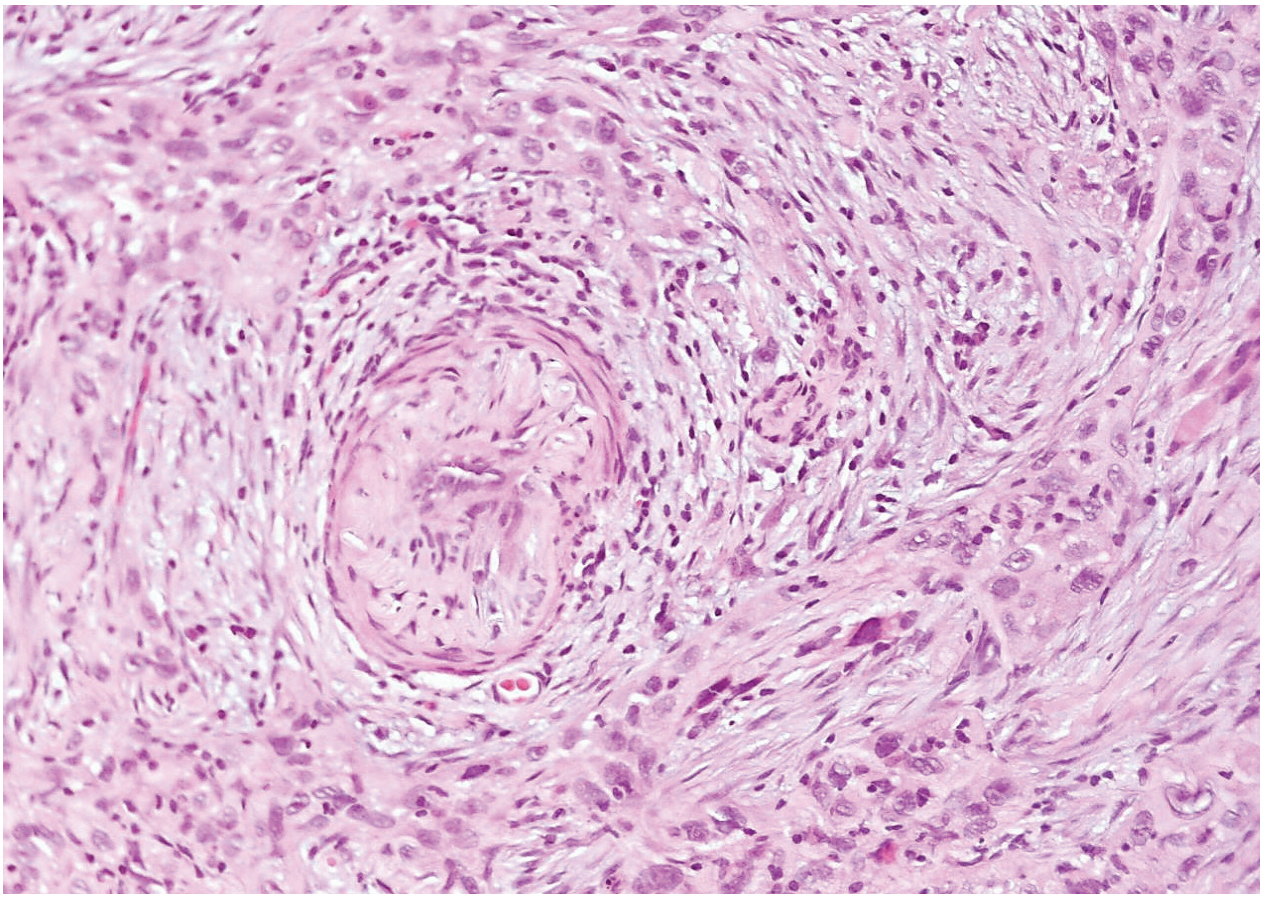

Figure 3: Tumour infiltration around a medium-sized blood vessel highlighting a vague fascicular growth pattern. Fusiform spindled cells are predominant while occasional epithelioid cells with prominent nucleoli are observed (hematoxylin-eosin staining, original magnification x200).

Immunohistochemical staining for S100 is negative within the tumour cells while highlighting extensive areas of perineural infiltration. Immuno-negativity by the neoplastic tumour cells was similarly obtained when stained with SMA; however, upregulated expression by the stromal cells was evident. A vague storiform to fascicular growth pattern is noted as shown in Figure 3.

DISCUSSION

The spindle cell variant of squamous cell carcinoma is a rare high-grade neoplasm synonymously referred to as sarcomatoid carcinoma. The WHO classifies SpCC as a malignant epithelial variant of SCC accounting for approximately 1% of all SCCs. It is biphasic in nature and has a high mortality rate due to its inherent aggressive biological nature and an increased propensity for metastases and recurrence. It is thus imperative for early recognition and treatment to successfully manage this neoplasm.[2] Early polypoid SpCC have a better prognosis than ulcerated or endophytic lesions detected at a later stage. SpCC is seldom if ever associated with high-risk human papillomavirus (HPV) regardless of the subsite of the head and neck involved by such a neoplasm.[9] SpCC of the head and neck is most often located within the larynx, trachea, hypopharynx, oesophagus, maxillary sinuses and orbits. Intra-oral SpCC is similarly rare in comparison to the prevalence of conventional SCC and has been documented to involve the tongue, buccal mucosa, attached gingiva and the lower lip.[1,2] The

Antibody	Clone	Manufacturer	Immunohistochemical staining pattern
AE1/AE3	AE1/AE3	DAKO, Glostrup, Denmark Pre-diluted	Strongly and diffusely positive within the overlying epithelium as well as within the lesional cells
P63	DAK-P63	DAKO, Glostrup, Denmark Pre-diluted	Strong diffuse nuclear signalling detected within tumour cell nuclei.
S100	Polyclonal	DAKO, Glostrup, Denmark Pre-diluted	Negative in lesional cells. Positivity highlights the extensive perineural infiltration.
SMA	HHF35	DAKO, Glostrup, Denmark Pre-diluted	Negative within neoplastic cells. Overexpression is noted by the myofibroblastic cells.

Table 1. Immunohistochemical staining in sections of tissue obtained from spindle cell carcinoma of the lower lip.

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lower lip as a site of involvement by conventional SCC is usually seen in patients with a history of occupational sun exposure.[16] Such an association was not provided in this case. SpCC occurring at mucosal sites are documented to have a higher prevalence in tissues which have undergone therapeutic irradiation and in patients who use tobacco and consume alcohol.[1,2] Furthermore, in addition to tobacco and alcohol use and a previous history of irradiation, poor oral health has been identified as a risk factor for the development of SpCC particularly in genetically susceptible individuals who simultaneously present with a combination of inflammation and injury.[17] SpCC shows a marked demographic difference with a male:female of 11:1 while occurring in the 6th to 7th decades.[2] Oral squamous cell carcinoma (OSCC) in its conventional form has a propensity for demographically presenting in older male patients in the 5th to 7th decades and are etiologically linked to tobacco use and alcohol consumption, representing the seventh most common malignancy globally.[16] The patient in this case report fits very well with the reported demographics of both SpCC and conventional OSCC. It should also be noted that the patient is RVD-reactive, the immunosuppression of which is known to predispose patients to the development of HIV-associated malignancies as well as those which are not defined specifically as HIV-associated. This may be attributed to decreased immune surveillance as well as immune dysfunction.[18] This patient has multiple risk factors which favour the development of OSCC; however, it is most unusual to encounter an SpCC on the lower lip.

Spindle cell carcinoma is one of several variants of SCC which have been described based on their unique histopathological features.[19] These include verrucous carcinoma, basaloid SCC, Papillary SCC, Adenosquamous carcinoma, Adenoid/Acantholytic SCC, carcinoma cuniculatum and spindle cell (sarcomatoid) carcinoma.[19-21] These neoplasms not only have unique microscopic features but are prognostically significant to recognise.[19]

SpCC has a unique clinical presentation in up to 90% of laryngeal or pharyngeal neoplasms in which lesions tend to present as polypoid, exophytic masses which project into the lumen. Lesions occurring within the oral cavity have a more variable morphology with 50 to 60% being exophytic. There is frequently extensive surface ulceration. In up to 80% of cases, at least a focus of conventional SCC is visible at some point within the lesion which may necessitate multiple serial sections of tissue.[1] The spindle cell component, however, most often predominates. The recognisable portion of conventional squamous cell carcinoma may be seen as a focus of epithelial dysplasia, carcinoma-in-situ or frankly invasive SCC which curiously tends to be identified within the stalk of the polyp. The spindle cells tend to be atypical and markedly pleomorphic occurring in association with atypical mitotic figures.[2,3,7,10] Various growth patterns have been identified with some lesions showing a storiform pattern of growth with irregular fascicle formation.[22] Occasional neoplasms have a myxoid appearance, often with extensive surface ulceration and sparsely distributed cells. Lesions in which discohesive tumour cells are identified may be diagnostically challenging as they frequently mimic exuberant granulation tissue. The spindle cell component in SpCC may mimic a true sarcoma although being of epithelial origin. Historical studies have shown that the morphological, immunohistochemical, ultrastructural and molecular features of SpCC show marked genetic similarity between the epithelial and spindled cells as noted in biphasic tumours. This serves to confirm divergent differentiation of the spindled cells from which is otherwise a true carcinoma.[1,19] Lesions with a predominantly monophasic spindled histomorphology tend to hinder accurate diagnosis.[1] The spindle or sarcomatoid component of SpCC occurring in the upper aerodigestive tract may be misdiagnosed as a variety of other spindle cell lesions, particularly malignant lesions, due to the inherent and frankly malignant nature of the neoplasm. However, there may be some morphological overlap with benign lesions in the differential diagnosis. The differential diagnosis for malignant neoplasms includes spindle cell melanoma, angiosarcoma, Kaposi sarcoma, synovial sarcoma and malignant peripheral nerve sheath tumour. Low-grade to benign lesions to be considered in the differential diagnosis include nodular fasciitis, inflammatory myofibroblastic tumour and solitary fibrous tumour.[1,5]

Without evidence of origin from overlying dysplastic surface epithelium or admixed nested epithelial cells, immunohistochemistry is required to confirm the diagnosis. In most cases there will always be at least focal positivity for immunohistochemical staining. AE1/AE3 or pancytokeratins is positive in up to 62% of cases while Epithelial Membrane Antigen (EMA) is positive in up to 47% of cases. P63 is regarded as an additional immunohistochemical marker with positivity being as high as 63%. A rate of 68% immunopostivity is reported when at least one epithelial marker is used but this increases to 79% if a combination of AE1/AE3, EMA and p63 are used. The recent recognition of p40 may improve these statistics; however, there are still many cases which fail to demonstrate positivity with a cytokeratin which perpetuates the diagnostic difficulty.[3] Almost all (100%) cases are positive for Vimentin with a small proportion of cases (up to 33%) showing positivity to either smooth muscle actin (SMA) or muscle specific actin (MSA).[1-3,19]

The unique polypoid clinical presentation at specific subsites, the co-expression of cytokeratins and Vimentin, evidence of origin from overlying epithelium and serial sections showing biphasic areas of squamous differentiation should allow for the diagnosis of SpCC and for distinction from possible malignant differentials. The frankly malignant histopathological features of SpCC generally allows for easy distinction from benign mesenchymal neoplasms. The increased expression of SMA within the stroma, as was noted in this case, is indicative of tumour-stroma crosstalk which occurs when the neoplastic cells secrete angiogenic and growth factors which stimulate the growth of the surrounding fibroblastic stromal cells and vascular cells which allows for the development of a self-sustaining vasculature. In turn, the upregulated stromal cells produce growth factors which further stimulate the neoplastic cells. The presence of such a tumour micro-environment serves to promote tumour growth and metastatic spread.[23] This property alone accounts for a poorer prognosis when present. Furthermore, SpCC inherently displays the properties of divergent differentiation from an epithelial to mesenchymal lineage in a process termed epithelial-mesenchymal transition. This dynamic process causes a change in the cellular morphology of the tissue of origin and suppression of epithelial characteristics, coupled with the acquisition of cell motility, reduced cell death by apoptosis and increased resistance to chemotherapeutic drugs which

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enhances the invasiveness and propensity for metastatic spread of the neoplastic cells.[24] Wide surgical resection remains the treatment of choice for SpCC.[6]

CONCLUSION

Spindle cell carcinoma is a rare variant of squamous cell carcinoma with a small percentage of cases located within the upper aerodigestive tract. The oral cavity is involved far less frequently than are the larynx, hypopharynx, orbits or maxillary sinuses. This case report aims to raise awareness of this unusual variant of SCC when considering the differential diagnosis of malignant spindle cell neoplasms which occur at this site. This requires a high index of suspicion, patience in searching for evidence of origin from overlying epithelium and the use of immunohistochemistry to expedite the diagnosis and initiate the most appropriate treatment.

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