GENERAL

spindle cell squamous cell carcinoma

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Introduction

Spindle cell squamous cell carcinoma (SCSCC) is an uncommon but clinically significant variant of squamous cell carcinoma that blends epithelial and mesenchymal characteristics. Though it represents only a small fraction of all squamous neoplasms, its aggressive behavior and diagnostic challenges make it a topic of growing interest among pathologists, oncologists, and surgeons alike. This comprehensive guide delves into the biology, clinical presentation, diagnostic workup, treatment strategies, and prognostic outlook for SCSCC, providing a clear roadmap for healthcare professionals and patients navigating this complex disease.

What Is Spindle Cell Squamous Cell Carcinoma?

Spindle cell squamous cell carcinoma is a biphasic tumor that displays both squamous epithelial cells and spindle-shaped mesenchymal cells. The spindle cells mimic fibroblasts or smooth muscle cells, giving the tumor a sarcomatoid appearance under the microscope. Despite its sarcomatous morphology, the malignant cells originate from squamous epithelium and often retain keratinizing potential, which is a hallmark of classic squamous cell carcinoma.

Histopathological Features

- Cellular morphology: The tumor exhibits sheets or nests of elongated, spindle-shaped cells with tapered ends, interspersed with pleomorphic squamous cells that may form keratin pearls.
- Stromal reaction: A desmoplastic stroma is common, sometimes containing abundant collagen fibers and inflammatory infiltrates.
- Mitotic activity: High mitotic rates and atypical mitoses are frequently observed, reflecting the tumor's aggressive nature.
- Necrosis: Coagulative necrosis can be present, especially in larger lesions.

Immunohistochemical Profile

Immunohistochemistry (IHC) is essential for confirming the diagnosis and excluding mimickers. Typical findings include:

- Positive markers: Cytokeratin AE1/AE3, p63, and high molecular weight cytokeratins highlight the epithelial component.
- Spindle cell markers: Vimentin positivity confirms the mesenchymal phenotype.
- Negative markers: S100, desmin, and smooth muscle actin are usually negative, helping to rule out melanoma, leiomyosarcoma, and other spindle cell tumors.

Clinical Presentation and Epidemiology

Spindle cell squamous cell carcinoma most often arises in the head and neck region, particularly the oral cavity, larynx, and pharynx. It can also present in cutaneous sites, especially on sun exposed skin, and rarely in the esophagus or other mucosal surfaces.

Key demographic and risk factors include:

- Age: The median age of diagnosis is 65–70 years.
- Sex: Slight male predominance (approximately 60% male).
- Smoking and alcohol: Strong associations with tobacco use and chronic alcohol consumption.
- UV exposure: For cutaneous lesions, cumulative sun exposure is a significant risk factor.
- Human papillomavirus (HPV): HPV 16 has been implicated in some head and neck cases, though its role in SCSCC remains less clear than in conventional SCC.

Patients typically present with a rapidly enlarging mass, ulceration, pain, or functional impairment such as dysphagia, hoarseness, or facial nerve involvement. The aggressive growth pattern often leads to early regional lymph node metastasis.

Diagnostic Workup

Accurate diagnosis of SCSCC hinges on a combination of clinical assessment, imaging, histopathology, and immunohistochemistry. Early identification is crucial because the therapeutic approach differs from that of conventional squamous cell carcinoma.

Imaging Modalities

- Computed Tomography (CT): Provides detailed information on bone erosion and soft tissue extension.
- Magnetic Resonance Imaging (MRI): Superior for delineating soft tissue involvement and perineural spread.
- Positron Emission Tomography (PET CT): Useful for staging, detecting distant metastases, and assessing metabolic activity.

Biopsy and Pathology

Incisional or excisional biopsy is the gold standard. Pathologists examine the specimen for biphasic morphology and perform a panel of IHC stains to confirm the diagnosis. It is essential to obtain adequate tissue to evaluate both epithelial and spindle components.

Differential Diagnosis

- Spindle cell carcinoma (sarcomatoid carcinoma): Similar morphology but often lacks keratinization.
- Spindle cell melanoma: Positive for S100 and SOX10; usually negative for cytokeratins.
- Leiomyosarcoma: Positive for desmin and smooth muscle actin.
- Fibrosarcoma or malignant fibrous histiocytoma: Lack epithelial markers.
- Metastatic carcinoma with sarcomatoid features: Requires correlation with clinical history.

Treatment Options

Management of spindle cell squamous cell carcinoma requires a multidisciplinary approach. Treatment decisions are guided by tumor stage, location, patient comorbidities, and functional outcomes. Below are the main therapeutic modalities.

Surgical Management

Wide local excision with clear margins remains the cornerstone of therapy for accessible lesions. Depending on tumor size and depth, procedures may range from simple excision to complex reconstructive surgeries involving free flaps or prosthetic devices. Neck dissection is often indicated when regional lymph nodes are clinically involved or when imaging suggests nodal disease.

Radiation Therapy

External beam radiation is frequently employed as adjuvant therapy after surgery, particularly for high grade tumors

or when margins are close. In unresectable or metastatic settings, definitive radiation can provide palliation and local control. Dose protocols typically range from 60–70 /Gy in 2 /Gy fractions.

Systemic Therapy

Standard chemotherapy regimens for squamous cell carcinoma—such as cisplatin plus 5 fluorouracil—are often applied to SCSCC. However, due to the sarcomatoid component, response rates can be variable. Targeted agents and immunotherapies are emerging as promising options.

Emerging Therapies

- Immune Checkpoint Inhibitors: Pembrolizumab and nivolumab have shown activity in head and neck squamous cell carcinoma and may benefit SCSCC patients with high PD L1 expression.
- Tyrosine Kinase Inhibitors: Agents targeting VEGF or EGFR pathways have been explored in case reports.
- Combination Strategies: Concurrent chemoradiation with checkpoint blockade is under investigation in clinical trials.

Prognosis and Outcomes

Spindle cell squamous cell carcinoma is generally associated with a poorer prognosis compared to conventional SCC, primarily due to its aggressive biology and tendency for early metastasis. Key prognostic factors include:

- Tumor stage: Advanced T stage correlates with reduced survival.
- Margin status: Positive or close margins increase recurrence risk.
- Lymph node involvement: Nodal metastasis is a strong predictor of mortality.
- Histologic grade: Poorly differentiated tumors have worse outcomes.
- Patient performance status: Comorbidities and overall health influence treatment tolerance.

Five year overall survival rates for SCSCC range from 30% to 50%, depending on stage and treatment modality. Early detection and aggressive multimodal therapy are essential to improve these figures.

Case Studies and Clinical Trials

Several case reports highlight the variability in presentation and response to therapy. For instance, a 68 year old male with a spindle cell SCC of the tongue underwent partial glossectomy followed by adjuvant chemoradiation and remained disease free at 18 months. Another case involved a cutaneous SCSCC on the lower leg that metastasized to the lungs; the patient received palliative radiation and immunotherapy, achieving a partial response lasting 6 months.

Clinical trials specifically targeting SCSCC are limited, but ongoing studies in head and neck squamous cell carcinoma often enroll patients with sarcomatoid variants. Key trials include:

- KEYNOTE 040: Evaluated pembrolizumab versus investigator chosen therapy in recurrent/metastatic head and neck SCC.
- CheckMate 141: Assessed nivolumab in patients with platinum refractory disease.
- EMPOWER HNSCC: Investigated cemiplimab in advanced head and neck SCC.

These studies provide insight into potential benefits of immunotherapy for spindle cell variants, though dedicated trials are needed.

Patient Support and Resources

- National Cancer Institute (NCI): Offers patient guides on head and neck cancers.

- American Cancer Society (ACS): Provides information on treatment options and coping strategies.
- Head and Neck Cancer Foundation: Offers counseling, support groups, and financial assistance.
- Patient Advocacy Networks: Online forums where patients share experiences and treatment outcomes.

Conclusion

Spindle cell squamous cell carcinoma, though rare, presents a formidable challenge due to its aggressive

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