# Sarcomatoid Lesions of Head and Neck Region: A Diagnostic Dilemma

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***Authors' contributions***

*This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.*

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## ABSTRACT

One challenging feature of head and neck pathology is that a dizzying array of sarcomatoid lesions occurs here ranging all the way from reactive to malignant and very aggressive. This makes accurate diagnosis critical. These lesions are quite diverse with great clinical and biological heterogeneity. Some are malignant while many others are benign or simply reactive in nature. For example; at mucosal sites, a well known lesion is spindle cell carcinoma (SpCC), which are overtly malignant, and the differential diagnosis then includes a number of different malignant spindle cell lesions. However, there are several benign or even non-neoplastic lesions that can sometimes be difficult to discern from SpCC, e.g. Nodular fasciitis, Proliferative myositis, Cellular schwannoma, Benign fibrous histiocytoma, Carcino sarcoma, Sarcomatoid melanoma. Fracture callus, etc.
**Aim of Study:** There is a diagnostic challenge to the oral pathologists to differentiate dizzying array of sarcoma like lesions from other similar microscopic simulates ranging all the way from

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reactive to malignant and very aggressive. This article aims to review the sarcomatoid lesions of the head and neck region with emphasis on differential diagnosis histologically and immunohistochemicaly.

## 1. INTRODUCTION

Sarcomatoid lesion of head and neck include a diverse group of clinically and biologically heterogeneous lesions. Some are malignant while many others are benign or simply reactive in nature. There is a diagnostic challenge to the oral pathologists to differentiate dizzying array of spindle cell lesions from other similar microscopic simulates ranging all the way from reactive to malignant and very aggressive. This article aims to review the sarcomatoid lesions of the head and neck region with emphasis on differential diagnosis histologically and immunohistochemicaly.

Sarcomatoid lesions generally found in head and neck region are as follows

> Nodular Fascitis
> Proliferative Myositis
> Spindle Cell Carcinoma
> Cellular Schwannoma
> Benign Fibrous Histiocytoma
> Carcino sarcoma
> Sarcomatoid Melanoma
> Fracture Callus

## 2. METHODS

### 2.1 Design

This review was conducted according to the Preferred Reporting Items for Systematic Reviews.

### 2.2 Literature Search Strategy

An extensive literature search for relevant original research studies was performed using PubMed‑Medline, Scopus, CINAHL, Web of Science, and other journals to find studies that have discussed about diagnosis of sarcomatoid lesion. The search was limited to specific criteria of spindle cell lesions, any age group, publication language (English), and publication year (1980–2020).

### 2.3 Selection Criteria

Articles with case studies, case reports, posters, and narrative literature reviews were included as they fulfill the criteria. All the articles (titles and abstracts) were initially independently screened by two reviewers and articles that discussed sarcomatoid lesion were included in the full content review. The exclusion criteria were articles that malignancy like sarcoma and carcinoma.

## 3. RESULTS

Two hundred and one articles were identified through the combined literature search. One hundred and thirty seven duplicate articles were removed. The title and abstract of 18 studies were assessed and excluded as they did not meet the inclusion criteria. The full text of additional 3 studies were reviewed and excluded as they were found not meeting the review criteria (studies done from 1980 to 2020, sarcomatoid lesion). Finally, 43 articles were included in the systematic review.

## 4. DISCUSSION

### 4.1 Nodular Fascitis

Nodular fasciitis, first described by Konwaler and Weiss in 1955 [1]. It is also known as pseudosarcomatous fasciitis, pseudosarcomatous fibromatosis and infiltrative fasciitis. It is one of the most under-diagnosed lesion and can be confused with spindle cell sarcoma, fibromatosis, fibrous histiocytoma, proliferative fasciitis, benign nerve sheath tumors, and pleomorphic adenoma because of features such as short history, rapid growth, marked infiltration, and somewhat similar histopathological picture. It mostly presents as a solitary, painless, and rapidly growing nodule usually of less than 3 months duration [2].

The etiology is still unknown after a good number of cases that are reported worldwide. It is considered to occur due to unusual proliferation of myofibroblasts triggered by local injury or inflammatory process. Although antecedent history of trauma has been implicated but its strong correlation with the disease occurrence has not been proven till date. It is commonly seen in the 40-50-year age group with almost

equal distribution amongst both genders. The most commonly affected sites are upper extremity and trunk followed in the decreasing order by head and neck and lower extremity. Nodular fasciitis has to be clearly distinguished from spindle cell sarcoma on the basis of degree of cytologic atypia which distinguished from fibromatosis (desmoid tumor) that shows dense collagenous stroma usually lacking myxoid areas along the with absence of extravasated RBCs. The fibrous histiocytoma (dermatofibroma) also forms an important differential diagnosis of nodular fasciitis showing spindle cell proliferation admixed with epithelioid histiocytes but it also lacks prominent vasculature and extravasated RBCs. An ill-defined tumor growing along the fibrous septa (interlobular distribution) with large myofibroblasts admixed with immature fibroblast like spindle cells in a myxoid or collagenous background stroma but devoid of extravasated RBCs points toward the diagnosis of proliferative fasciitis. Benign nerve sheath tumors such as schwannoma and neurofibroma are also important differential diagnosis of nodular fasciitis that can be diagnosed on histology by the presence of Antoni A and Antoni B patterns of growth in schwannoma and abundance of collagen and little myxoid material in neurofibroma. Also neurofibroma lacks extravasated RBCs, frequently seen in nodular fasciitis [3].

Immunohistochemically, it shows positive reactivity with Smooth muscle actin, Muscle specific actin and Calponin, and shows negative reactivity with Desmin, H-caldesmon, S100, Sox10, CD34, ERG, Epithelial membrane antigen, keratin. When its became difficult to differentiate from other lesion, we can do diagnosis by IHC. For example spindle cell carcinoma is positive for cytokeratin but for nodular fascitis it is non reactive [4].

## 4.2 Proliferative Myositis

Proliferative myositis (PM) is a pseudosarcomatous, benign, fibroblastic proliferation with atypical giant cells resembling ganglion cells. It is a rapidly growing lesion and infiltrates skeletal muscles in diffuse manner [5]. It is a skeletal muscle counterpart of proliferative fasciitis, which arises from superficial fascia and is relatively superficial in location. It most commonly affects skeletal muscles of shoulder, thorax, and thigh, uncommon sites are tongue and oral cavity [6]. Majority of the patients are seen to below 5th decades of life, but it may be seen in children also. It can be easily misdiagnosed with Rhabdomyosarcoma and ganglioneuroblastoma, especially in younger age group. It is usually diagnosed on histopathology, as clinical findings are non specific [7].
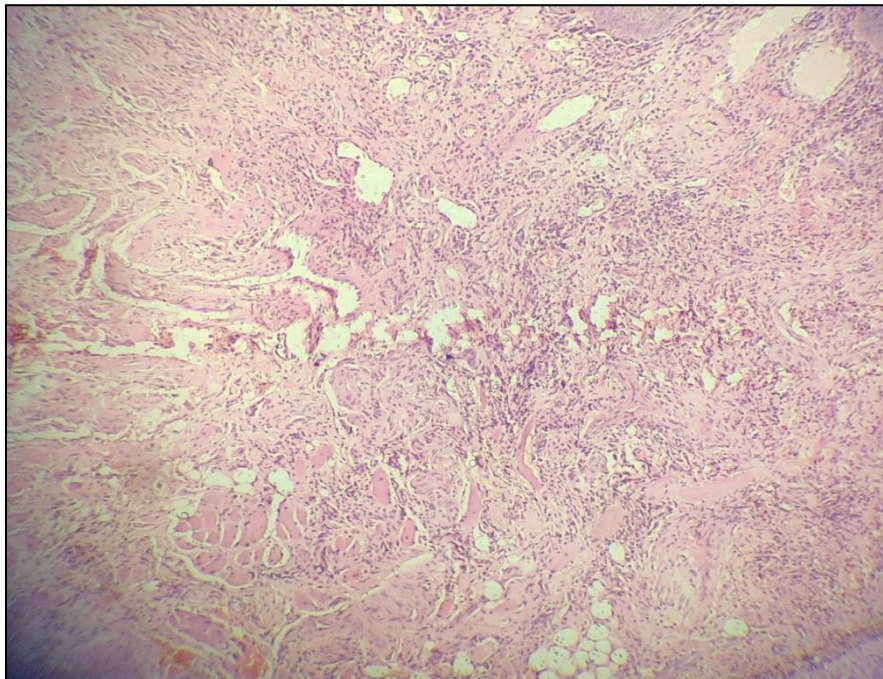


**Fig. 1. Photomicrograph showing spindle shaped cells, hypercellularity, and multinucleated giants cells (H&E, 100X)**

Spindle cell lesions with overlapping histologic features with PM include nodular fasciitis, desmoid fibromatosis, or adult-type fibrosarcoma. Giant/bizarre ganglion-like cells may be sometimes confused with rhabdomyoblasts in rhabdomyosarcoma, or ganglion cells and neuroblasts in ganglioneuroblastoma [8].

Nodular fasciitis typically tend to show a well-demarcated border, whereas PM commonly shows an infiltrative border. Spindle cells in nodular fasciitis resemble those in PM due to their shared myofibroblastic nature, but nodular fasciitis lacks giant ganglion-like cells.

Desmoid fibromatosis is a poorly demarcated tumor composed of spindle-shaped myofibroblasts arranged in sweeping fascicles without giant ganglion-like cells. So it can be differentiated on that basis histologically [8].

Giant ganglion-like cells in proliferative myositis may mimic and be mistaken for sarcomas, most commonly rhabdomyosarcoma or ganglio-neuroblastoma. In proliferative myositis ganglion-like cells lack cross-striations and show more cytoplasmic basophilia than that of rhabdomyoblasts [8].

Ganglioneuroblastoma comprises of fascicles of Schwann cells with variable numbers of ganglion cells, resembling proliferative myositis in a limited biopsy. Immunohistochemistry is very helpful to distinguish these entities [8].

Adult-type fibrosarcoma is a non-pleomorphic spindle cell sarcoma, commonly in the deep soft tissue of extremity or trunk. The lesion is typically composed of spindle cells arranged in parallel or herringbone pattern, without ganglion-like cells. Spindle cells in adult-type fibrosarcoma are more cellular than that of proliferative myositis [8].

### 4.3 Immunohistochemistry

Immunohistochemical stains may be helpful when the histological findings are undetermined. The findings in PM and differential diagnosis are summarized in below table [9-12].

**Table 1. Immunohistochemistry of proliferative myositis and the differential diagnosis**

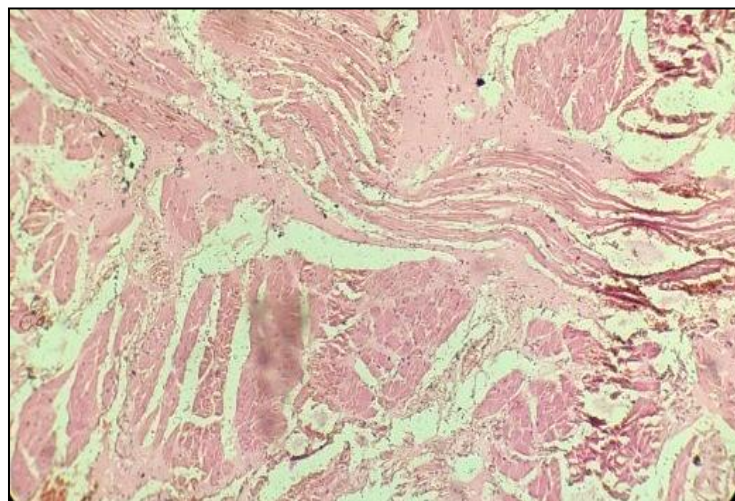| Immunohistochemistry Marker | Proliferative Myositis | Nodular Fascitis | Desmoid Fibromatosis | Rhabdomyo-sarcoma | Ganglioneuro-blastoma |
|---|---|---|---|---|---|
| SMA | + | + | + | Variable | _ |
| MSA | + | + | + | Variable | _ |
| VIMENTIN | + | + | + | + | _ |
| KERATIN | _ | _ | _ | Rarely | _ |
| S100 | _ | _ | _ | _ | + |
| DESMIN | _ | _ | Rarely | + | _ |
| MYOGENIN | _ | _ | _ | + | _ |
| BETA -CATENIN | _ | _ | +(Nucleus) | _ | |



**Fig. 2. Photomicrograph showing spindle shaped fibroblasts and ganglion like cells with skeletal muscle fibres (H&E, 100X)**

## 4.4 Spindle Cell Carcinoma

Spindle Cell Carcinoma (SpCC) is a variant of squamous cell carcinoma which has spindled or pleomorphic tumor cells which simulate a true sarcoma but are epithelial in nature. Most SpCC are biphasic tumors. In other words, they are composed of both a conventional squamous cell carcinoma and a spindle cell or pleomorphic component. However, as many as one-third are monophasic spindled or pleomorphic tumors making the diagnosis of carcinoma more difficult [13].

The larynx, particularly the glottis, is the most common primary site followed by the oral cavity, specifically the tongue, floor of mouth, and gingivae [14].

A unique clinical and pathologic feature of SpCC is its macroscopic growth pattern. Greater than 90% of laryngeal and pharyngeal tumors present as polypoid and exophytic masses projecting into the lumen [15,16,17].

The exophytic masses are usually smooth, dark brown, and lobulated with extensive mucosal ulceration. SpCC are biphasic tumors with areas of conventional squamous cell carcinoma admixed with areas of spindled and/or pleomorphic tumor [18]. The spindled component usually predominates. The Squamous component can be either show focal dysplasia, carcinoma in situ, or frankly invasive squamous cell carcinoma. This latter component is usually present in the stalk of the polyp, at the deepest aspect or advancing front of the tumor. When dysplastic squamous epithelium remains on the surface, the spindle cells frequently can be seen ''dropping off'' from its basal layer [15]. The spindled cells may be bland and regular or may be markedly pleomorphic with multinucleated giant tumor cells. There may be a wide variety of patterns including fascicular, storeiform, lacelike, or myxoid and on occasion, truly definable sarcomatous differentiation, such as osteosarcomatous, chrondrosarcomatous, or rhabdomyosarcomatous, may be seen. Typically, the spindle cell component is more haphazard than most true sarcomas, with irregular fascicle formation. Sometimes, ''transition-type'' cells with a morphology in-between the carcinoma and spindled component are seen. These cells are epithelioid but not nested. Some SpCC will present as extensively ulcerated masses with tumor cells widely spaced apart in a loose, pale or myxoid background. There are frequently abundant small vessels with plump endothelial cells and numerous inflammatory cells, particularly neutrophils. These SpCC can closely mimic exuberant granulation tissue. Finally, another pitfall is where the spindle cell component demonstrates loss of cohesion of the tumor cells and consequently mimics an angiosarcoma. This has been described in other body sites as pseudoangiosarcomatouscarcinoma and has also been reported in oral cavity SpCC [19]. Mitotic activity can vary, but averages more than one per high power field with a range from 0 to over 10. Atypical mitoses are common. Immunohistochemistry has been extensively analyzed in SpCC [13].

Obviously key to the diagnosis is the confirmation of epithelial differentiation in the spindle cells. Most, but unfortunately not all, cases of SpCC will show staining for one or more epithelial markers, likes AE1/AE3 or pancytokeratin,. Epithelial membrane antigen (EMA) and p63, was positive for SpCC [18,20]. SpCC has been shown to be positive for mesenchymal-type markers as well. Virtually 100% of cases are positive for vimentin and a significant minority for smooth muscle actin (31–33%) and muscle specific actin (15–42%) [21].

## 4.5 Cellular Schwannoma

Cellular schwannoma is an uncommon variant of schwannomas, which accounts for approximately 4.6% of the benign peripheral nerve sheath tumors and predominately affects middle-aged adults. It was first described by Woodruff et al. [22].

Most case of schwannoma shows no symptoms and are diagnosed incidentally. Large tumors can show symptoms related to its mass effect. Although cellular schwannoma is a well-recognized variant of schwannomas with more than 200 reported cases, it remains difficult to diagnose and can be misdiagnosed as other tumors, such as the well-differentiated malignant peripheral nerve sheath tumor, leiomyosarcoma, fibrosarcoma, Melanotic schwannoma, or solitary fibrous tumor [23,24]. Histologically, cellular schwannoma is a well-circumscribed or encapsulated mass. Signs of hemorrhage are common, but cystic degeneration is uncommon. Cellular schwannomas differ from ordinary schwannomas by presence of only hypercellular Antony A areas. The presence of thick fibrous capsules, hyaline thick-walled vessels, and S-

100 positive cells in cellular schwannoma enable the distinction from a low-grade malignant peripheral nerve sheath tumor or a leiomyosarcoma [25].

## 4.6 Benign Fibrous Histiocytoma

The benign fibrous histiocytoma (BFH) is a mesenchymal benign neoplasm composed of fibroblasts and histiocytes arising in the cutaneous and noncutaneous soft tissues [26].

BFH is seen mainly in adults and most frequently in young and middle aged women, usually under 50 years of age and have a history of sun exposure, trauma, or chronic infection, indicating BFH as a reactive disease [27].

Pathologic analysis and diagnosis of this type of lesions is often challenging and usually based on a combination of light microscopy and immunohistochemistry [28].
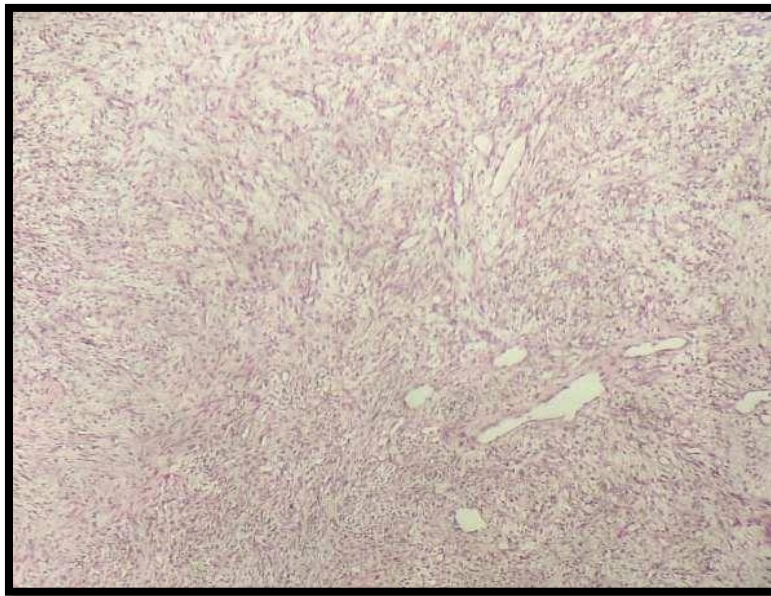


**Fig. 3. (H&E, 100X) showing malignant spindle cells with hyper chromatic nuclei, arranged in fascicles or whorled pattern**
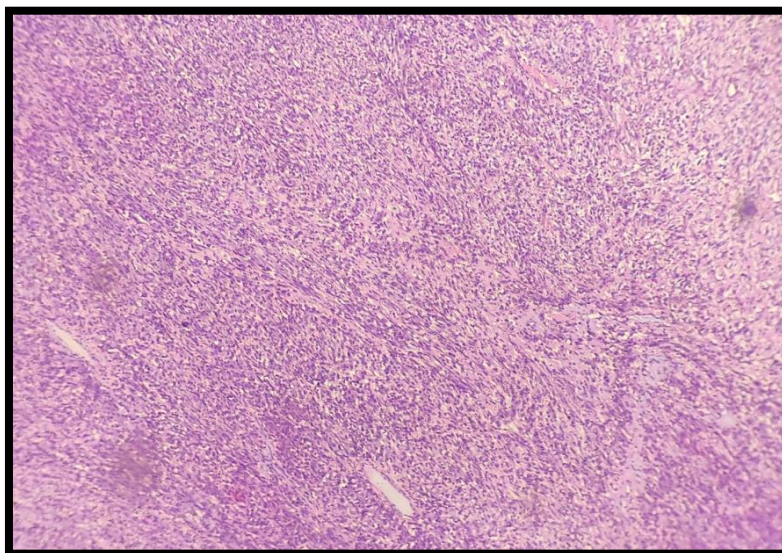


**Fig. 4. (H & E, Mag 100X), showing hypercellular antoni a areas comprising of hyperchromatic dense spindle shaped cells**

The benign fibrous histiocytoma has been a controversial because of its dilematic histogenesis. Immunohistochemical staining and ultrastructural studies of the tumours and cell lines derived from them has revealed features of myoblastic and histiocytic differentiation of mesenchymal origin. Immunostaining for CD68 can be found in any tumour-containing lysosomal granules or phagolysosomes [28]. BFH typically shows a biphasic cell population of histiocytes and fibroblasts [29]. In some cases the cells resemble myofibroblasts, primitive mesenchymal cells, and cells having intermediate or mixed features. Other histological features frequently described in BFH are the presence of multinucleated giant cells, abundant vascularity, and inflammatory infiltrate. The main differential diagnosis of oral BFH includes nodular fasciitis, solitary fibrous tumour, neurofibroma, and dermatofibroma CD34 positivity is a useful aid for distinction between benign fibrous histiocytoma and solitary fibrous tumour the former reported asusually negative [30].

Differentiation between BFH and nodular fasciitis can be based on S-100 positivity, more frequent mitoses and different fascicle configuration for the latter [31]. BFH and dermatofibroma show similar immunoreactivity. The negativity for SMA and S-100 could differentiate the lesion from leiomyosarcoma and neurogenic tumours [32,33].

## 4.7 Carcinosarcoma

Carcinosarcoma is a highly malignant tumor characterized by dual malignant histologic differentiation of the epithelial component consisting of a focally squamous cell carcinoma and a mesenchymal component having a sarcomatoid stroma [34,35]. In the head and neck region, the pharynx and larynx are most common sites, followed by the esophagus, the oral cavity and the nasal area [34].

Histologically the lesion consisted of malignant epithelial and mesenchymal components. The two components are generally not demarketed by transition zone. The epithelial element remains generally well‑differentiated squamous cell carcinoma with the formation of epithelial pearls, but poorly differentiated and non‑keratinizing squamous cell carcinoma areas are found, with cells forming sheets, cords, and bundles separated by varying amounts of vascular connective tissue. The mesenchymal component shows sarcoma‑like, malignant features, including hypercellularity, marked pleomorphism, and enlarged nuclei. Reticulin is positive for vascular connective tissue. Malignant epithelial cells present in connective tissue shows positivity for p63, epithelial components can be easily identified by cytokeratin and mesenchymal components can be identified by vimentin, S-100, actin, desmin etc. [36].
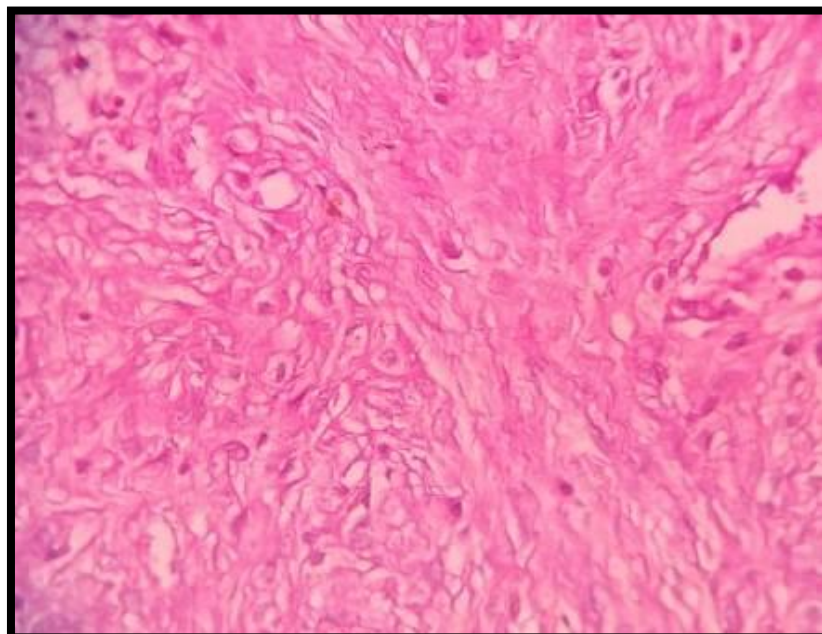


**Fig. 5. (H & E, Mag 100X), showing proliferating fibroblast and histiocytes, arranged in short interlacing fascicles**
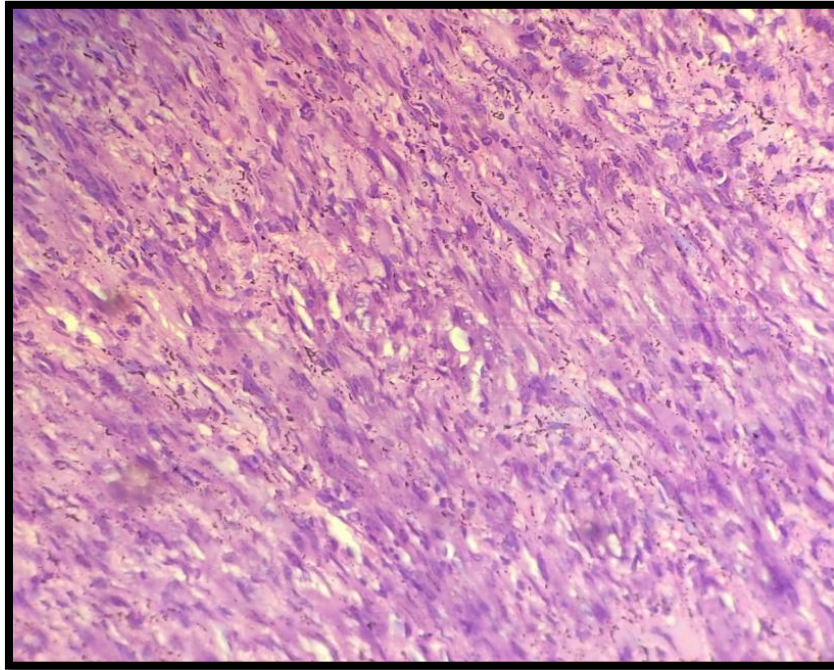
**Fig. 6. (H & E, 100X) showing sarcoma part of carcinosarcoma, having spindle shaped cells arrand=ged in fascicles**

## 4.8 Sarcomatoid Melanoma

Sarcomatoid melanoma is a rare type of melanoma lacking typical histologic features of melanoma and often lacks expression of S100 protein and melanocyte-specific markers. Given the rarity of this entity, its clinicopathologic findings are not well defined. Lesions shows ulcerated, pedunculated, highly cellular proliferations of atypical spindle cells arranged as fascicles and/or sheets [37].

Sarcomatoid melanoma has a wide range of differential diagnosis, which includes, sarcomatoid/ spindle-cell squamous cell carcinoma, superficial malignant peripheral nerve sheath tumor, atypical fibroxanthoma, pleomorphic dermal sarcoma, spindle-cell melanoma, and desmoplastic melanoma [37].

Histopathologically, all these entities are composed of variably pleomorphic, mitotically active atypical neoplastic cells with large vesicular nuclei and a variable amount of eosinophilic cytoplasm. Thus, distinction requires careful histologic examination, especially at the tumor periphery, accompanied by judicious use of IHC [37].

In sarcomatoid squamous cell carcinoma, associated with actinic keratosis, Squamous cell carcinoma may be present in or nearby adjacent or attached epidermis [38]. Sarcomatoid squamous cell carcinomas typically show at least focal staining for cytokeratins and/or p63 or p40 [39,40].

Superficial malignant peripheral nerve sheath tumors tend to present at a younger age, and may present in children and young adults of 30 years old [41]. Superficial malignant peripheral nerve sheath tumors are associated with neurofibromatosis 1 in less than 40% of cases [42]. Histologically and immunophenotypically, there is significant overlap between sarcomatoid melanoma and malignant peripheral nerve sheath tumor. Both are weakly positive or even negative for S100 protein. For many pathologists, making a diagnosis of superficial malignant peripheral nerve sheath tumor requires the presence of a neurofibroma or associated peripheral nerve [43]. However, the lessio is seen arising from a nerve or neurofibroma, focus should beon the nuclei of neoplastic cells that will be wavy and tapered, and the neoplasm displays alternating cellular and myxoid areas [41]. Superficial malignant peripheral nerve sheath tumor usually has a remnant of a precursor neurofibroma [42]. Therefore, like sarcomatoid melanoma, examining the periphery of the tumor for the precursor lesion is of ultimate significance [8].

Distinguishing sarcomatoid melanoma from spindle-cell melanoma and desmoplastic melanoma requires recognition of the dedifferentiated sarcomatoid component. Sarcomatoid melanoma lacks the nested pattern that is often present in spindle-cell melanoma, and the spindle-cell component of sarcomatoid melanoma loses immunophenotypic evidence of melanocytic differentiation, including diminished to negative expression of S100 protein. Desmoplastic melanoma is much less cellular and has strong expression of S100 protein [37].

## 4.9 Fracture Callus

Reactive or proliferative lesions of bone and periosteum may at time mimic osteocartilaginous malignancies. Fracture repair encompasses all of the classic stages of wound healing, with the additional formation of osteocartilaginous callus. Histologically, the early callus is reminiscent of disorganized fetal cartilage and bone, and many signaling and regulatory pathways active in skeletogenesis are expressed in fracture callus. As a consequence, at different phases callus may have immature fibroblastic, chondroblastic, and osteoblastic cells mimicking lesions like fibrosarcoma, chondrosarcoma, or osteosarcoma. Familiarity with the clinical presentation, radiologic appearance, and characteristic histologic findings will prevent the unfortunate misdiagnosis of these lesions. Since the late 1980's MR imaging has become the modality of choice for the assessment of musculoskeletal disorders. However, with the advancement of CT technology through development of multidetector scanners, CT scan is again gaining importance in the evaluation of musculoskeletal diseases. It should be noted that radiographs should be always performed as the primary investigation and still remain a cornerstone in imaging. Some authors believe that MRI and CT can be useful to distinguish hyperplastic callus from Osteosarcoma in doubtful cases [43].

## 5. CONCLUSION

There are numerous atypical sarcoma like lesions which can be present along the head and neck region. Because it is so dilemmatic, pathologists should strongly consider and ruled out before diagnosing one of the less common lesions. With attention to the clinical scenario, careful evaluation the H&E morphologic features, and judicious use of immunostains, one can work through these difficult cases to arrive at the correct diagnosis.

## CONSENT

It is not applicable.

## ETHICAL APPROVAL

It is not applicable.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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