Mesenchymal Chondrosarcoma in the Central Nervous System: Histological Diagnosis

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Abstract

Mesenchymal chondrosarcoma is a rare malignant neoplasm typically arising in the bones of young adults. It may also arise in somatic soft tissue, central nervous system and other organs. There are no specific clinical or radiological characteristics, and histological assessment remains the key to diagnosis. Histological features are similar regardless of site, and display a characteristic biphasic pattern composed of highly undifferentiated small round cells and islands of well differentiated hyaline cartilage. In this chapter, we discuss the clinical, radiological and histological features of mesenchymal chondrosarcoma arising in the central nervous system (CNS), the important differential diagnoses of small round cell tumour within the CNS, and the differentiating features of mesenchymal chondrosarcoma from Ewing sarcoma/PNET, medulloblastoma, haemangiopericytoma, monophasic synovial sarcoma and atypical teratoid/rhabdoid tumour.

Introduction

Mesenchymal chondrosarcoma is an aggressive tumour mostly, but not exclusively, involving the skeletal system of adolescents and young adults. Involvement of the central nervous system is extremely rare, and has only been acknowledged by isolated case reports. Primary cartilaginous tumours account for 0.16% of all intracranial

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neoplasms, and these include chondromas, chondrosarcomas, myxoid chondrosarcomas, and mesenchymal chondrosarcomas. Mesenchymal chondrosarcoma has a propensity for local aggressiveness and frequent recurrence, and is considered one of the most malignant subtypes of chondrosarcoma (Bingaman et al. 2000).

The characteristic biphasic histological appearance has been widely described, composing of an undifferentiated small round cell proliferation and islands of cartilaginous differentiation. Diagnostic complexities arise when only one of the two characteristic components is sampled for histological examination. The anatomical and radiological features, histological characteristics, the phenomenon of post-chemotherapy cytomaturation, as well as differential diagnoses of small round cell tumours within the central nervous system are discussed.

Epidemiology/Sites of Involvement

Mesenchymal chondrosarcoma is a rare aggressive malignancy which usually affects young adults in their second to third decades with equal gender distribution (Fletcher et al. 2002; Unni et al. 2005). It was first described by Lichtenstein and Bernstein (1959), and has traditionally been regarded as a neoplasm of bone. However, extraosseous examples involving areas such as somatic soft tissues, mediastinum, orbit, and meninges have been reported in the literature in recent years (Unni and Inwards 2010; Bingaman et al. 2000), and the central nervous system (CNS) is now considered the most common site of extraosseous mesenchymal chondrosacroma (Louis et al. 2007). The CNS can be involved by direct extension from a nearby osseous primary (cranial or spinal), a lesion of dural origin, or by arising directly within the brain parenchyma (Burger and Scheithauer 2007). The most common location of mesenchymal chondrosarcoma within the central nervous system is the craniospinal meninges (Fig. 7.1), and most cases are supratentorial, located in the frontoparietal region (Chen et al. 2004).

Clinical Presentation

The clinical presentation of intracranial mesenchymal chondrosarcoma is similar to those of other mass lesions within the CNS.

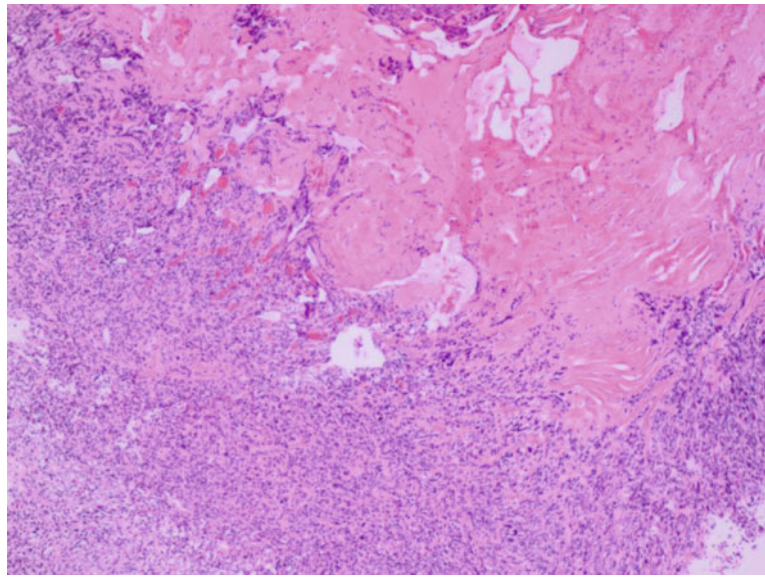

Fig. 7.1 Low power view showed the *small round blue* cell component of the mesenchymal chondrosarcoma attached to the dura mater (H&E, ×20)

Symptoms and signs are dependent on the location of the tumour, and frequently reflected the compressive effects of involved neurological structures, with examples including cranial nerve palsies in tumours involving the base of skull. Most patients have a tendency to present with headaches and other symptoms related to increased intracranial pressure (Scheithauer and Rubinstein 1978), and isolated cases may only be detected after the discovery of metastatic disease.

Radiological Features

Imaging of intracranial mesenchymal chondrosarcoma show inconsistent features, however, the majority of cases are hypointense to normointense on T1-weighted MRI, with strong enhancement after administration of gadolinium (Huang et al. 2004). It can be extremely hypervascular on angiography, and embolisation may be required prior to surgery. Due to its common involvement of the meninges and strong enhancement on MRI, these tumours may resemble malignant meningioma or haemangiopericytoma on radiological imaging (Chen et al. 2004).

Histopathology

Pathological examination of both extraosseous and osseous examples shows the same characteristic biphasic appearance (Scheithauer and Rubinstein 1978). The two distinct elements include islands of hyaline cartilage and a proliferation of undifferentiated small round cells (Fig. 7.2). The cartilaginous component is well differentiated and may appear as benign hyaline cartilage, low-grade chondrosarcoma, and rarely, as an intermediate-grade chondrosarcoma (Unni et al. 2005). The undifferentiated areas show sheets or alveolar arrangements of small round cells with relatively uniform nuclei, dense chromatin and sparse cytoplasm (Fletcher et al. 2002; Unni et al. 2005; Louis et al. 2007). Staghorn vascular spaces are commonly seen. The two characteristic components have a tendency to show an abrupt transition, however, occasional cases may show a gradual merging of the two elements. More importantly, the proportion of each element is highly variable and diagnostic problems arise when a limited biopsy only shows one component (Bingaman et al. 2000; Lin et al. 2012).

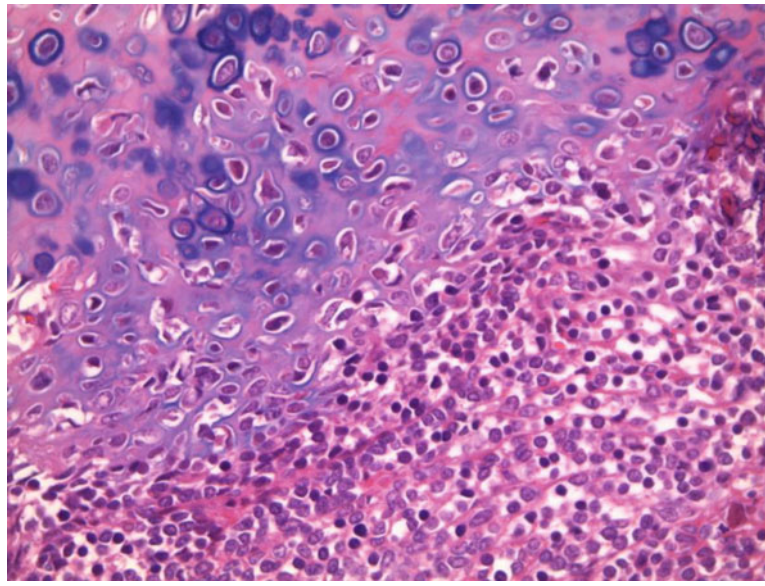

Fig. 7.2 Section showed the characteristic biphasic histological appearance, with islands of hyaline cartilage juxtaposed against a *small round blue* cell population (H&E, ×200)

Histochemical and Immunoperoxidase Studies

Histochemical and immunoperoxidase studies of mesenchymal chondrosarcoma are not specifically helpful in distinguishing it from other differential diagnoses. The small cells are glycogen rich (Burger and Scheithauer 2007), and stain positively for CD99, vimentin and Leu7. The chondroid cells are positive for S100 (Fletcher et al. 2002). Sox9, a master regulator of chondrogenesis, has been shown in a study by Wehrli et al. (2003) to reliably differentiate mesenchymal chondrosarcoma from other small round blue cell tumours, based on the hypothesis that both small cell and cartilaginous components are derived from primitive chondroprogenitor cells. In their study, 21 of 22 cases of mesenchymal chondrosarcoma showed positive nuclear staining in both components, and the remaining 73 small round blue cell tumours (including rhabdomyosarcoma, neuroblastoma, Ewing sarcoma/PNET, lymphoma, small cell carcinoma, merkel cell carcinoma, small cell osteosarcoma, extraskeletal myxoid chondrosarcoma and small cell desmoplastic tumour) displayed negative staining. Hence, Sox9 may be an useful ancillary stain for diagnosing mesenchymal chondrosarcoma when an undifferentiated small round cell component is present with a lack of chondroid elements.

Ancillary Tests

Electron microscopy of the undifferentiated small cells show large nuclei and little organelles, similar to primitive mesenchymal cells, and the cartilaginous areas show a usual chondrocyte appearance (Fletcher et al. 2002; Unni et al. 2005). No specific molecular aberration has been identified, although an identical Robertsonian translocation involving chromosomes 13 and 21 [der(13;21)(q10;q10)] has been detected in two cases (Fletcher et al. 2002; Unni et al. 2005).

Diagnostic Complexities

As mentioned previously, the proportion of the two components is highly unpredictable and the predominance of either component may result in diagnostic difficulties. The dominance of cartilaginous component may lead to a misdiagnosis of a pure chondroid lesion, and the sole presence of the small round cell component may result in the erroneous diagnosis of other small round cell tumours. Even if the tumour contained both elements in significant amounts, diagnostic dilemma may arise if only one element is sampled in a limited biopsy or debulking procedure.

Furthermore, a recent case report by Lin et al. (2012) highlighted a diagnostic pitfall in the diagnosis of mesenchymal chondrosarcoma arising from the tentorium cerebelli of a 21 year old woman. Histological examination of the tissue obtained at the initial debulking procedure demonstrated a dural-based pure small round cell population with hyperchromatic ovoid cells, finely to coarsely granular chromatin, inconspicuous nucleoli and scanty cytoplasm. The cells were Periodic acid Schiff (PAS) positive and diastase sensitive, and immunohistochemically showed focal strong membranous immunoreactivity with CD99, and negative staining for epithelial markers. The diagnosis of Ewing sarcoma/primitive neuroectodermal tumour (PNET) was made and the patient underwent chemotherapy and radiotherapy according to a PNET protocol. However, the tissue obtained during a definitive complete macroscopic removal several months after the initial procedure showed prominent hypercellular lobules of atypical chondroid cells, prompting the re-diagnosis as a mesenchymal chondrosarcoma. This case highlighted diagnostic complexities of mesenchymal chondrosarcomas in an intracranial location where limited biopsy material is often obtained, and potential misdiagnosis if only one component is sampled. The authors also raised a second hypothesis of post-chemotherapy cellular maturation in an attempt to explain the differences in histological appearances seen in the tissue obtained from the first and second procedure.

Post-chemotherapy cellular maturation is a well known phenomenon described in a range of pediatric tumours, including pediatric sarcomas and embryonal tumours, Wilms' tumour and germ cell tumours (McCartney et al. 1984; Omar et al. 1986; Coffin et al. 2005; Smith et al. 2002; Nozza et al. 2010). This phenomenon is thought to be a secondary event to anti-cancer agents selectively destroying immature and more anaplastic clones, and hence, offering relatively benign and mature cells a survival advantage (McCartney et al. 1984; Omar et al. 1986). The post-chemotherapy cyto-maturation phenomenon may potentially explain the marked differentiation of the cartilaginous component in this case.

Differential Diagnoses

A small round cell tumour arising in the brain raises several differential diagnoses. These include Ewing sarcoma/PNET, medulloblastoma, haemangiopericytoma, monophasic synovial sarcoma and atypical teratoid/rhabdoid tumour. Firstly, Ewing sarcoma/PNET has a tendency to affect a younger population, with the peak incidence in the second decade (Louis et al. 2007). Secondly, most reported primary CNS Ewing sarcoma/PNET are extra-axial, dural based masses (Theeler et al. 2009). Histologically, the small round cell appearance in Ewing sarcoma/PNET show a striking histological similarity to mesenchymal chondrosarcoma, both exhibiting sheets of small round cells with PAS-positive, diastase sensitive, glycogen rich cytoplasm (Louis et al. 2007; Burger and Scheithauer 2007). Homer-Wright rosettes may be helpful in distinguishing Ewing sarcoma/PNET, however it is only present in occasional cases. Furthermore, CD99, a characteristic immunoperoxidase stain positive in Ewing sarcoma/PNET, may also be seen in other tumours such as mesenchymal chondrosarcoma, haemangiopericytoma and synovial sarcoma (Louis et al. 2007; Kazmi et al. 2007). As a result of these non-specific features, there is an increasing reliance on the utilisation of molecular testing, and these include reverse transcription polymerase chain reaction (rt-PCR) looking for EWS-FLI1 and EWS-ERG (or other EWS variant) fusion transcript, and fluorescence in-situ hybridisation studies (FISH), looking for characteristic chromosomal translocation t(11;22)(q24;q12) or other variant translocations, such as t(21;22)(q22;q12) (Louis et al. 2007; Kazmi et al. 2007). Sensitivities and specificities of 91 and 100% respectively have been reported with FISH, and this is considered a confirmatory test if positive (Kazmi et al. 2007). However, it is noted that 5% of these tumours have no detectable chromosomal translocation and in these cases, making the correct diagnosis may be challenging (Navarro et al. 2007).

Medulloblastoma is also another important differential diagnosis, as it shows sheets of similar round blue cells, and Homer Wright rosettes are only present in less than 40% of cases. However, it rarely shows a dural-based location, and has an absence of glycogen rich cytoplasm and CD99 positivity (Theeler et al. 2009; Kazmi et al. 2007). Haemangiopericytoma is similarly meningeal-based, and typically displays characteristic staghorn vessels, which may be seen in mesenchymal chondrosarcoma (Kazmi et al. 2007). However, they have different immunophenotype, with haemangiopericytoma being Factor XIIIa and CD34 positive. Monophasic synovial sarcoma may also display a prominent haemangiopericytomatous vascular pattern, cytokeratin and EMA positivity, and SYT locus rearrangement on FISH (Fletcher et al. 2002). Atypical teratoid/rhabdoid tumour shows presence of rhabdoid cells, EMA positivity and distinctive loss of INI-1 nuclear expression (Louis et al. 2007).

In conclusion, mesenchymal chondrosarcoma is a malignant neoplasm rarely encountered in the central nervous system. Clinical experience with cranial or spinal mesenchymal chondrosarcoma is limited, but frequent local recurrence and distant metastasis is the norm. Mesenchymal chondrosarcoma should be considered in the differential diagnosis of any small round blue cell lesion encountered in a dural-based or parenchymal lesion, and correlation with the clinical and radiological information is mandatory,

especially to ascertain whether the entire lesion has been removed. Obtaining adequate material displaying both components, performing the appropriate immunoperoxidase panel and molecular testing to exclude other conditions, and a high index of suspicion is the mainstay to diagnosis.

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