Answers to QUIZ 1, 2, & 3

Answer to Quiz 1:

Malignant Melanoma of Soft Tissues (Clear cell sarcoma)

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This neoplasm was first described by Enzinger in 1965 as clear cell sarcoma of tendons and aponeuroses[1]. However, irrefutable evidence of melanogenesis in the tumour has been provided in several subsequent studies[2-7]. At present, most authorities believe that the tumour is in fact a malignant melanoma of soft tissues and is of neural crest origin, although its precise histogenesis remains uncertain[8-12].

The tumour is relatively rare , usually affects adolescents and young adults, almost always in an extremity, most commonly the leg, where the foot and knee are preferred sites. It arises from the deep soft tissues, usually from deep aponeuroses, tendons or fascia, but may involve the overlying soft tissues and skin secondarily. There is commonly a protracted history of swelling, accompanied by pain in approximately half of the cases. After treatment, which primarily consists of radical surgery, the course of disease is often characterized by local recurrences and metastasis to regional lymph nodes and distant sites, especially the lungs and the skeleton. A relatively protracted course of disease and an ultimately poor prognosis are characteristic.

Histological features include nests and strands of oval or elongated cells, separated by fibrous septa. The tumour cells have centrally located, often vesicular nuclei and a moderate to large amount of pale or granular-amphophilic cytoplasm. A small amount of melanin is usually present in some cases; this tumour is positive for S-100 protein regardless of the presence or absence of melanin. Ultrastructurally, melanosomes may be demonstrated. Mitotic figures are scarce and may even be absent in some instances. Multinucleated tumour cells are present in about half of the cases[13].

The diagnosis of melanoma of soft parts is based on a combination of these characteristic histological features complemented, as in the present case, with positive immunohistochemical staining for S-100 protein and melanoma-specific antigens such as HMB45[11]. Immunohistochemically this tumour[13] shows the same features as cutaneous malignant melanoma[14], and hence distinction from metastatic melanoma may sometimes depend on clinical features. Seven of the 24 cases studied by Mooi et al (1995) have shown expression of keratins using CAM 5.2, LP34 and MNF 116 antibodies[13]. No clinical or histological differences were seen in these seven cases when compared with the 17 keratin negative cases.

Histological differential diagnosis include a number of soft tissue sarcomas[13], notably synovial sarcoma, which shares some of its clinical and morphological features. In difficult cases immunohistochemistry is essential, since soft tissue melanoma is generally positive for S-100 protein and HMB45. Synovial sarcoma shows focal staining for epithelial markers such as Epithelial Membrane Antigen and keratin, while staining for S-100 protein and HMB45 are negative. It is important to note that focal and weak immunoreactivity for keratin in itself should not constitute proof against a diagnosis of melanoma of soft tissue or metastatic melanoma, because primary cutaneous melanoma cells also express keratin at low levels[13, 14].

Focal and weak expression of keratin is seen in a variety of bone and soft tissue sarcomas, such as

Ewing's sarcoma, leiomyosarcoma and malignant fibrous histiocytoma. It is also worth remembering that other sarcomas with epithelioid features (such as chordoma, malignant peripheral nerve sheath tumour and epithelioid sarcoma) may exhibit prominent keratin staining[13, 15]. In fact as many as 28 non-epithelial tumour types have been reported to express keratins[15].

REFERENCES:

1. Enzinger F M. Clear-cell sarcoma of tendons and aponeuroses. An analysis of 21 cases. Cancer 1965; 18:1163-1174.

2. Hoffman G J and Carter D. Clear cell sarcoma of tendons and aponeuroses with melanin. Archives of Pathology 1973; 95: 22-25.

3. Mackenzie D H. Clear cell sarcoma of tendons and aponeuroses with melanin production. Journal of Pathology 1974; 114: 231-235.

4. Bearman R M, Noe J, Kempson R L. Clear cell sarcoma with melanin pigment. Cancer 1975; 36: 997-984.

5. Boudreaux D, Waisman J. Clear cell sarcoma with melanogenesis. Cancer 1978; 41: 1387- 1394.

6. Toe T K and Saw D. Clear cell sarcoma with melanin. Report of two cases. Cancer 197; 41: 235-238.

7. Ekfors T O, Rantakokko Y. Clear cell sarcoma of tendons and aponeuroses: Malignant melanoma of soft tissue? Pathology in Research and Practice 1979; 165: 422-428.

8. Chung E B and Enzinger F M. Malignant melanoma of soft parts. A reassessment of clear cell sarcoma. Am J Surgical Pathol 1983; 7:405-413.

9. Kindblom L-J, Lodding P and Angervall L. Clear cell sarcoma of tendons and aponeuroses An immunohistochemical and electron microscopic analysis indicating neural crest origin. Virchows Archives A Pathological Anatomy 1983; 401: 109-128.

10. Mukai M, Torikata C, Iri h et al. Histogenesis of Clear cell sarcoma of tendons and aponeuroses. An electron microscopic, biochemical, enzyme histochemical and immunohistochemical study. Am J Pathol 1984; 114: 264-272.

11. Swanson P E and Wick M R. Clear cell sarcoma. An immunohistochemical analysis of six cases and comparison with other epithelioid neoplasms of soft tissue. Arch Pathol and Lab Med 1989; 113: 55-60.

12. Fletcher C D M and McKee P H. Progress in malignant soft tissue tumours. In Fletcher C D M and McKee P H (Editors) Pathology of soft tissue tumours. Churchill Livingstone, Edinburgh, 1990; 302-303.

13. Mooi W J, Deenik W, Peterse J L and Hogendoorn P C W. Keratin immunoreactivity in melanoma of soft parts (clear cell sarcoma). Histopathology 1995; 27: 61-65.

14. Bishop P W, Menasce L P, Yates A J, Win N A and Banerjee S S. An immunophenotypic survey of malignant melanomas. Histopathology 1993; 23: 159-166.

15. Schaafsma H E and Ramaekers F C S. Cytokeratin subtyping in normal and neoplastic epithelia: basic principles and diagnostic application. Pathol. Annu. 1994; 29: 21-62.

Answer to Quiz 2:

Angiolymphoid Hyperplasia with Eosinophilia (Epithelioid Haemangioma)

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This case is an example of recurrent angio-lymphoid hyperplasia with eosinophilia (ALHE) involving subcutaneous fibrous tissue and striated muscle of upper forehead. ALHE is a rare disease of the skin and subcutaneous tissue with a predilection for the head and neck region. Less frequently, involvement of other sites including a case within skeletal muscle has been reported. In 1969, Wells & Whimster for the first time in the English literatue reported this unusual subcutaneous angiomatoid lesion in the head and neck region of nine cases under the designation 'angiolymphoid hyperplasia with eosinophilia'. They suggested that this disease might have an early vascular and a late lymphoid stage and that the latter might correspond to Kimura's disease. Subsequently, ALHE and Kimura's disease have often been considered to be the same disease, but recent reports suggest that ALHE and Kimura's

disease are different clinico-pathological entities. ALHE has been described under the same or other names, however, the designation 'epithelioid haemangioma', coined by Enzinger & Weiss (1983) has gained considerable popularity implying that ALHE is a benign vascular neoplasm. It has predominantly been reported in Caucasians of either sexes, in the 3rd to 5th decades. Patients only occasionally have a circulating eosinophilia or an associated lymphadenopathy. The lesions not infrequently recur after local excision.

Kimura's disease (or perhaps more appropriately Kim's disease) was first described in the Chinese literature in 1937 by Kim and Szeto, who reported seven cases under the designation 'eosinophilic hyperplastic lymphogranuloma' (Kung & Chan 1988). Kimura's disease is a recurrent mass lesion that occurs predominantly in Orientals, shows a very marked predilection for males and typically presents in adolescence or early adulthood affecting the subcutaneous tissues, major salivary glands and lymph nodes. The majority of cases have an associated lymphadenopathy and circulating eosinophilia.

Distinctive histological features of ALHE are exuberant proliferation of vessels lined by cuboidal to hobnail endothelial cells with irregular nuclei and cytoplasmic vacuoles, fibromyxoid matrix, involvement of muscular coat of blood vessels and zonation of inflammatory infiltrate towards the peripheral portion of the lesion.

Distinctive features of Kimura's disease are florid lymphoid infiltrate, with prominent lymphoid follicles, vascularization and or necrosis of germinal centers with marked eosinophilia often with eosinophil abscess formation, proliferation of high endothelial venules, and sclerosis.

These histological features has suggested that epitheliod haemangioma is a proliferation of atypical endothelial cells, possibly neoplastic, that is associated with a variable inflammatory infiltrate, whereas Kimura's disease is primarily an inflammatory condition in which high endothelial venules are usually found.

The angiomatoid lesion lined by cuboidal endothelial cells with prominent nuclei (Fig.4) and many endothelial cells with cytoplasmic vacuoles (not illustrated) were present in our case. Large vascular branches with thick walls, and fibromyxoid changes were absent. However, certain important histopathological features of Kimura's disease described above such as vascularization and necrosis of germinal centers, marked eosinophilia and eosinophil abscess formation were not found in multiple sections examined. High endothelial venules were frequent. Peripheral blood did not show any eosinophilia.

REFERENCES:

1. Fletcher C D M and McKee P H. Progress in benign soft tissue tumours. In Fletcher C D M and McKee (Editors) Pathology of soft tissue tumours. Churchill Livingstone, Edinburgh, 1990; 252-256.

2. Chan J K C, Hui P K, Ng C S, Yuen N W F, Kung I T M, qnd Gwi E. Epithelioid haemangioma (angiolymphoid hyperplasia with eosinophilia) and Kimura's disease in Chinese. Histopathology 1989; 15: 557-574.

3. Akosa A B, ALI M K, Khoo C T K and Evans D M. Angiolymphoid hyperplasia with eosinophilia associated with tetanus toxoid vaccination. Histopathology 1990; 16: 589-593.

4. Kuo T, Shih L-Y, and Chan H-L. Kimura's sisease. Involvement of the regional lymph nodes and distinction from angiolymphoid hyperplasia with eosinophilia. American J Surg Pathol 1988; 12: 843-854.

5. Kung I T M and Chan J K C. Kimura's disease or Kimm's disease? (Letter to the Editor). American J Surg Pathol 1988; 12: 804-805.