

1. STUDIES ON MULTIPLE MYELOMA

Declaration

Seven studies are submitted in this division, six of which (2 –7) were initiated by myself and one by the late Professor J Dauth (1). I was responsible as fifth author in the first study (1) for the microscopic analyses and relevant discussion only. In the second study (2), I collected the data and performed the evaluation of the light microscopic and ultrastructural features and prepared the manuscript, Dauth and de Coning did the biochemistry, Jordaan performed the biopsy and du Toit did the autopsy. I prepared the manuscript in study (3) and Lello and Fayman took the biopsies and assisted with the writing of the paragraph on the surgical management of the cases. Dauth, Dvornak and Senekal performed the biochemical analyses and provided inputs on the evaluation thereof. The ultrastructural interpretation in study (4) was done by myself, Dauth assisted with the biochemical interpretation and van Wilpe performed the electron microscopy. Study (5) was written edited by me, Dauth provided inputs on the biochemical- and Pretorius the clinical manifestations of the cases. I collected the data and prepared the manuscripts in studies (6) and (7). In both, Dauth contributed to the biochemical analyses of the cases whereas in study (7) van Heerden performed the statistical analysis and van der Walt performed the salivary immunodiffusion analytic technique.

Abstract

The orofacial manifestations of multiple myeloma in an African population sample had never been reported in the literature. Study (1) stimulated the authors interest in the unique and up to that stage unreported tumorous orofacial manifestation of multiple myeloma. Another two patients with the same orofacial features were subsequently recorded in study (3) and the principles in the management thereof established. The structural crystalline inclusions in the nuclei of the neoplastic plasma cells in study (2) formed the basis of an ultrastructural investigation of 10 cases of multiple myeloma presented in study (4). Ultrastructural diagnostic features, which characterize neoplastic plasma cells, were described including nuclear-cytoplasmic asynchrony and erytrophagocytosis. Distention of the rough endoplasmic reticulum with accumulation of colloid was shown in the plasma cells of a non-secretor myeloma in study (5) and a hypothesis on the pathogenesis thereof presented. Amyloidosis, a complication of multiple myeloma, was investigated with light- and electron microscopic techniques in tongue biopsies of 30 patients suffering multiple myeloma (6). The findings established the tongue as a common site for amyloidogenesis. It was not possible to show a positive correlation between the percentage of plasma cells in bone marrow aspirates or the presence of urinary light chains and amyloidogenesis in multiple myeloma. Study (6) did not support the reported higher amyloidogenic potential of lambda light chains. Study (7) compared immunoglobulin concentrations in mixed saliva and blood of 24 myeloma patients (the largest series on immunoglobulin related proteins in saliva of myeloma patients reported). The authors failed to confirm depressed salivary immunoglobulin concentrations despite circulatory humoral immunoparesis. This study added an

interesting parameter to the debate on multiple myeloma induced selective immunoparesis and partially explains the paucity of opportunistic oral infections in patients suffering this disease.

2. STUDIES ON MINERALIZED TISSUES: BONE AND TEETH

Declaration

Fourteen publications are submitted in this section all of which were initiated and planned by myself. In study (8) Dauth and I wrote the manuscript, De Villiers prepared the graphics and Potgieter provided the clinical data and radiographs. Van Heerden and I prepared the manuscript of study (9) and Potgieter and Golele provided clinical information and radiographs. I analyzed the data and prepared the manuscripts in studies (10) and (11). In studies (12), (13) and (14) Nkhumeleni prepared the specimen for analyses and executed the literature reviews and Dauth, Van Heerden and myself analyzed the data and wrote the manuscripts. Smith performed and Pitout interpreted the amino acid analyses in study (12) and Turner and Dreyer performed the inorganic analyses in study (13) and Turner in study (14) respectively. I prepared the manuscript in study (15), Rama and Dreyer performed the inorganic analyses, Dauth assisted with the interpretation thereof and Brown and Smith interpreted and performed the organic analyses respectively. I wrote the manuscripts of studies (16), (17) and (18). Studies (15) and (16) are based on my PhD thesis. Bosman and Noffke edited the manuscript of study (16) and Vorster prepared the micrographs. The results of study (19) were partially used by Van Niekerk for the dissertation of his masters degree. Van Heerden, Van Niekerk and myself prepared the publication, De Vos provided the material and Turner

executed the ultra structural examination. I prepared the manuscript of study 20 and provided the material for study 21. I assisted with the writing of the latter manuscript.

Abstract

Technical difficulties encountered during the preparation of specimen of mineralized bone and teeth for analytical purposes are responsible for the paucity in the literature on the morphology, composition and metabolic induced changes affecting these tissue types. The abundance of material available to the author prompted this research program. Study (8) served as an introduction to the techniques employed in dynamic labeling of bone and the histomorphometric measurement thereof. After demonstrating that it was indeed possible to monitor osteoblastic-, osteoclastic- and mineralization activities in bone accurately, a histomorphometric diagnostic service was introduced. Study (9) emanated from service rendering in this field and established the value of histomorphometry in the diagnoses and management of rickets. Based on histomorphometric findings, rickets was divided in hypertrophic- and atrophic types, with specific diagnostic and prognostic implications. Study (10) propagated the use of histomorphometry in the diagnoses and monitoring of the responses to therapy of other metabolic bone disease states. A need for a review on the histopathologic changes in metabolic bone diseases arose which prompted study (11). This review was presented as invited guest speaker at the 10th International Association of Oral Pathology meeting in Guatemala, 2000.

Analytical studies on human teeth were initiated concomitantly. The amino acid composition of dentin was investigated in study (12) and two amino acids, identified for

the first time in human dentin, were recorded. In study (13) it was shown that there is a significant difference in the magnesium, fluoride and zinc contents between opaque and translucent dentin. Study (14) proved higher levels of mineralization of the tissue that occlude dentinal tubules than that between the tubules in translucent human dentine.

The potential of determining the geographic origin of elephant ivory (dentin) on the inorganic composition thereof was illustrated with the aid of atomic absorption spectrometry, inductively coupled plasma optical emission spectroscopy and ion selective electrodes in study (15). The histology of elephant ivory was described in study (16) and a theory on the histogenesis of the unique chequered pattern proposed. Studies (17) and (18) are detailed histologic descriptions of the intrauterine development of the tush (deciduous tusk) and tusk of the elephant. The analyses of data obtained on elephant tusklessness in the Kruger Park resulted in study (18), which proposed an explanation for differences reported in the incidence rates of tusklessness amongst different elephant populations in Africa. In study (19) the morphologic characteristics of the tush were recorded for the first time in the scientific literature. Study (20) demonstrated the weak tusks of the Kaokoveld elephant to be the result of a probable vitamin C deficiency. This hypothesis was based on the low level of hydrolyzed lysine found in Koakoveld ivory. Results obtained through nuclear microprobe analyses for trace elements in ivory validated the potential use of this technique for the determination of the geographic origin of ivory (21).

3. STUDIES ON SALIVARY GLANDS: NORMAL STRUCTURE AND NEOPLASTIC PROLIFERATIONS

Declaration

Ten publications are submitted in this section. Studies (22) to (25) and (30) were initiated and designed by me and studies (27) to (29) and (31) by Van Heerden. I collected the material, interpreted the light- and electron micrographs and prepared the manuscripts of studies (22) and (23). All authors were involved in the collection of specimen analyzed in study (22). Dreyer performed the biochemical analyses, Dauth assisted with the interpretation thereof and I prepared the manuscript. In study (25) I collected the material and prepared the manuscript with Van Niekerk, who also performed the electron microscopy. Thein provided some of the cases in study (26) and Van Heerden and I reviewed the microscopic sections and prepared the manuscript. In studies (27), (28) and (29) I participated in the analyses of the data and preparation of the manuscripts. Van Heerden and I prepared the manuscript of study (30) whereas I contributed to the material and participated in editing the manuscript of study (31).

Abstract

Study (22) followed on an invitation from the editor of Critical Reviews in Clinical Laboratory Sciences to prepare a review article on the myoepithelial cell. The manuscript was written at a stage when developments pertaining to myoepithelial cells

revolutionized the understanding of their involvement in pathologic processes. The manuscript was illustrated with, amongst others, micrographs of tissues collected from exocrine glands of the African elephant and buffalo. Study (23) focused on salivary myoepithelium and their differentiation in neoplasms of salivary gland origin.

The structure of the homocrine seromucinous parotid salivary gland of the African elephant and the composition of its saliva was established in study (24). Unique biochemical characteristics of elephant saliva, the first time reported on, include the absence of amylase and elevated concentrations of potassium, urea, calcium and phosphorus. In study (25) the influence of secretory pressure on myoepithelial development in the salivary system of the elephant was illustrated with the aid of scanning electronmicroscopy after enzymatic digestion of the basement membranes of the secretory apparatus.

Studies (26) to (31) investigated aspects of salivary gland neoplasia. In study (26) a polymorphous low grade adenocarcinoma with tyrosine crystalloids had been reported, refuting the claim that these deposits are unique to benign mixed tumors of salivary gland origin. The overlapping AgNOR count between various salivary gland neoplasms demonstrated in study (27) mitigated against the use of this technique as an absolute criterion in the diagnosis of this group of neoplasms. The largest series on intraoral salivary gland neoplasms reported in an African population sample at the date of publication appears under study (28). This study showed significant differences in the pattern and pathology of intraoral salivary gland neoplasms when compared with findings

in studies performed at other geographic locations. In a study encompassing DNA flow cytometry and AgNOR staining (29) a statistically insignificant but positive correlation was found between these techniques. The AgNOR technique, which is fast and cost effective, was recommended above flow cytometry to determine the proliferative activities of tissue of salivary gland neoplasms imbedded in wax.

During the early nineties new approaches to the diagnosis and classification of salivary gland neoplasms created confusion. This precipitated study (30) that attempted to clarify misconceptions and establish uniform diagnostic principles. In study (31) the clinico-pathologic features, immunohistochemistry and DNA ploidy status of a series of intraoral salivary duct carcinomas were reported. The tumors were found to be composed predominantly of ductal cells with prominent cytokeratin expression and the majority was found to be aneuploid. The value of the ploidy status in determining the prognosis of salivary duct carcinomas will however require a follow-up study of the patients presented.

4. DIAGNOSTIC INTERPRETATION OF JAW TUMORS AND CYSTS

Declaration

Studies (32), (34), (37), (38), (41), (46), and (48) were initiated and planned by me. In study (30) Van Heerden and I prepared the manuscript, Turner performed the sections for microscopic analyses and Mare provided the material. I was involved in the evaluation of the cases and preparation of the manuscript in study (33) and Weir and Kreidler

provided clinical data and radiographs. In study (34) Van Heerden assisted me in analyzing the data and preparing the manuscript whereas Seeliger interpreted the radiographs and Dreyer provided clinical data and treated the case. I contributed towards the preparation of the manuscripts in studies (35) and (36) and collected data and prepared the manuscript of study (37). Noffke interpreted the radiographs in the latter study. Van Heerden and myself analyzed the data and prepared the manuscripts in studies (38) and (39), Sitzman and Heymer provided clinical data and Turner performed the microscopic techniques. I participated in the analyses of the data and the preparation of the manuscript in study (40). Van Heerden and I analyzed the data and prepared the manuscript in study (41) and Kreidler provided the clinical information and radiographs. I translated the manuscripts of studies (42) and (43) from German into English and together with Van Heerden analyzed the pathological specimen and edited the final versions of both manuscripts. I participated in the analyses of the data and preparation of the manuscript in study (44). My role in study (45) was limited to the microscopic analyses of the case. Van Heerden and I analyzed the microscopic slides and prepared the manuscript in study (46) and Noffke interpreted the radiographs. I participated in the microscopic analyses and preparation of the manuscript in study (47). The microscopic appearances of the tumors in studies (48) and (49) were analyzed by me, Lello provided the clinical data in study (48), Noffke performed the radiographic analyses in study (49) and all the authors contributed to the preparation of the manuscripts. I did the microscopic examination and assisted in the preparation of the manuscript in study (50).

Abstract

Descriptions of odontogenic tumors in large mammals are unusual. Study (32) described the features of an odontoma in the mandible of an African elephant. The tumor was at the stage of publication the largest odontoma reported in the literature.

Studies (33) and (35) described the clinico-pathologic features of extremely large examples of ossifying fibroma and adenomatoid odontogenic tumor respectively. In study (33) a shift towards a greater fibrous tissue component at the expense of bone as well as an increased incidence of aneurysmal bone cyst formation in large ossifying fibromas were demonstrated. The large adenomatoid odontogenic tumors in study (34) proved unrestricted growth potential, thereby negating the hypothesis that they are hamartomatous rather than neoplastic in nature.

Studies (35), (36) and (37) described hitherto unreported syndromes, which exhibit multiple hamartomatous odontogenic fibroma-like proliferations. Studies (35) and (37) demonstrated the unique association between multiple unerupted teeth, enamel malformation and central odontogenic fibroma-like lesions. At the time of reporting, study (38) represented the fourth case of true peripheral dentinogenic ghost cell tumour reported in the English literature.

Studies (39) and (40) analyzed the clinico-pathologic features of glandular odontogenic cysts. Electron microscopy employed in study (39) showed a process morphologically similar to apoptosis in the epithelial lining of these cysts. Study (40) analyzed nine cases

of glandular odontogenic cyst, bringing the total number reported in the literature to 54. This study represents the most detailed radiological description of these cysts thus far and proposes a histopathologic overlap with the central type mucoepidermoid carcinoma.

Studies (41), (42) and (43) reported on the classification, differential diagnosis of dentigerous-like cysts and relative frequencies of cysts-like lesions affecting the jawbones. In study (41) new developments in the classification of odontogenic cysts of the jaws were reported. Pitfalls in the clinical diagnosis of dentigerous cyst-like lesions were highlighted in study (42). It was demonstrated that a significant percentage of lesions with a dentigerous appearance were in fact unicystic ameloblastomas or odontogenic keratocysts. This study emphasized the need for microscopic examination in order to establish an accurate diagnosis. In the extensive review of jaw cyst-like lesions in a German population sample (43), the presentation of unicystic ameloblastomas in a significantly higher age category than is generally reported, was demonstrated. The relative frequencies of jaw cysts in this population sample differ in many respects from our experience.

Ameloblastomas were analyzed in studies (44), (45) and (46). A retrospective study of 30 unicystic ameloblastomas (44) revealed their aggressive behavior as well as a need for thorough microscopic examination of the cyst wall in order to determine the extent of surgical removal. HPV type 18 DNA was found in a verrucous lesion within the lining of a locule in a polycystic ameloblastoma in study (45). Identification of the virus, which was considered to represent a secondary infection, was the first description of its kind in

an ameloblastoma. A detailed microscopic investigation of a series of 108 ameloblastomas (46) demonstrated clinico-pathological diversity in a significant number of tumors. The association of ameloblastomas with adenomatoid odontogenic tumor-like proliferations, ameloblastic fibroma- like areas, melanocytes, mucous- and squamous cell metaplasia and stromal desmoplasia amongst others were reported.

Study (47) reviewed the literature and reported a case of calcifying epithelial odontogenic tumor with intracranial extension. This study demonstrated the serious complications following neglect of a benign maxillary odontogenic neoplasm. Studies (48) and (49) highlighted the potential pitfalls in the diagnosis of low-grade osteosarcomas and extra nodal Hodgkins lymphomas of the jaws respectively. Study (50) reported on a rare case of tumoral calcinosis involving the temporomandibular joint, emphasizing the differential diagnosis thereof.