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Short Course 12

Advances in diagnostic electron microscopy

Chairperson: J **M** Nesland *Norway* **Co-chairpersons** J A Gnmaud *France* and J Lioreta *Spain*

Electron microscopy in analysis of skin diseases

W.H. Muss

Institute of Pathological Anatomy Landeskilniken Salzburg, Austria.

The advent and success of immunohistochemical and immunocytochemical techniques and, most recently, of biomolecular methods in the diagnosis of skin disorders might seem to render conventional transmission electron microscopical (CTEM) examinations of dermatological specimens to be old-fashioned. Assuming that 95% of dermatological diagnostic work is done by dermatohistopathologists correlating the patients' clinical appearance with the morphology of histological sections, the value of CTEM seems to be drastically reduced and the technique is continuously being replaced by modern ones such as immunoelectron microscopy (IEM) and/or biomolelcular techniques. Moreover, questions such as "CTEM, – and even EM – is it obsolete?" have been raised many times in the past years and most recently by leading scientists and experts in those techniques. Despite croaking about "EM is dead – Is EM dead?" EM and CTEM have several applications and certainly are very useful in the diagnosis and management of many dermatological entities, provided communication between pathologists, dermatologists and dermatohistopathologists defines exactly when and how one can make the maximum use of a diagnostic tool such as electron microscopy.

The short course "Electron Microscopy in Analysis of Skin Diseases" focuses mainly on tissue specimens either from the operating theater or sent in by practicing dermatologists and processed for CTEM in our hospital. The course covers methods of obtaining optimal specimens (including pitfalls); transport of specimens to the laboratory; rapid as well as classical specimen processing into resins; making and examining large area semithin resin sections, including applications of reliable polychromatic diagnostic staining; reembedding of paraffin sections or paraffinized specimen blocks into resin for CTEM; a range of entities of skin diseases where CTEM can be helpful, e.g., cases of bullous epidermolysis, some of which give a very uncommon result; screening for mucosis fungoides (Sezary cells) inepidermal infiltrates or peripheral blood specimens ("buffy coats"); Langerhan's cell histiocytosis (distinction between histiocytosis X and non histiocytosis X, *vs.* nevi); suspected tumor entities *e.g.,* malignant amelanotic melanoma; storage diseases, such as argyria, neuronal ceroid lipofuscinosis as manifested in skin specimens; viral diseases, *e.g.,* orf, purpura fulminans (disseminated intravascular coagulation, destruction of microvasculature by bacteria) and others. Due to time limitation, the topics cannot be covered as a whole nor given detailed descriptions and the intention is to present only a synopsis of the activities in our area. If time permits, hints on subsequent special immunoelectron microscopic methods, as well as some notes on useful internet links concerning literature search and EM image galleries in dermatopathology, will be given and discussed. Also, printed handouts concerning the matters discussed will be available at the lecture site.

The contemporary role of electron microscopy in the diagnosis of mitochondrial encephalomyopathies

K. Kyriacou[1] and T. Kyriakides2

tDept. of Electron Microscopy and Molecular Pathology and 2Dept. of Neurosciences, The Cyprus Institute of Neurology and Genetics, Nicosia, Cyprus.

Introduction

Mitochondrial diseases exhibit a wide spectrum of clinical phenotypes, which include pure myopathies as well as multisystem disorders involving major organs such as the brain, skeletal muscle, heart, kidney and liver (1, 2). The age of disease onset ranges from birth to old age and because of the frequent involvement of the central nervous system and muscles, the term mitochondrial encephalomyopathies (MEs) is often used to describe these disorders.

Historically the concept of a mitochondrial myopathy was first introduced by Luft *et al.* (3). Currently, the term mitochondrial disorder is used to describe diseases that are associated with defects in the oxidative phosphorylation system, particularly the ones that are caused by mutations in mitochondrial DNA (mtDNA).

During the 1960s, much diagnostic emphasis was given to the presence of "ragged red fibers" (RRF), visualized with the modified Gomori trichrome stain (4). RRF indicate proliferation of mitochondna, which usually appear as subsarcolemmal aggregates in cryostat sections of muscle fibers, It should be noted that RAE are not specific for primary MEs but can be found in various other neuromuscular disorders, as well as in old age (5). In spite of these limitations, the presence of ARE is still considered the histological hallmark of mitochondrial disorders. Subsequently, electron microscopy of muscle biopsies led to the recognition of different patterns of mitochondrial changes. Shy and Gonatas (6) first identified a case of "pleoconial myopathy", which was characterized by excessive proliferation of normal-looking mitochondria. This was followed by the description of "megaconial myopathy" in which greatly enlarged mitochondria with disoriented cristae were found in the biopsies of affected muscle fibers (7). Other ultrastructural