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Book Review

Malignant pleural mesothelioma: A guide for clinicians, A. Giordano, R. Franco, editors (Academic Press, Elsevier IncC, USA) 2019. 186 pages. Price. Not mentioned.
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Mesothelioma, a tumour strongly associated with occupational asbestos exposure, is a rare but aggressive malignancy. Owing to its initial nonspecific manifestation, mesothelioma is usually diagnosed at an advanced stage, and the tumour has limited therapeutic options. Its rarity and the variation in its geographic distribution is a major constraint in the field of research related to its therapeutics and prognostication. This book provides updated information on various aspects of this tumour which is of considerable practical value for understanding the disease and patient management. The book has seven chapters contributed by experts working in the field of oncology, chiefly from the European countries and the United States. Although the book deals primarily with malignant pleural mesothelioma (MPM) that accounts for approximately 90 per cent of cases, certain aspects discussed in it are pertinent to mesotheliomas involving other serous body cavities as well. The book begins with the 'preface' that effectively sums up the gravity of the problem, concluding with the need for utilizing the currently available research outcomes on mesothelioma for the future breakthroughs in its management.

The first chapter elaborates upon the data acquired through several epidemiological studies and touches upon health surveillance as well. Apart from the risk of mesothelioma linked to progressive, and past occupational exposures to asbestos, the chapter brings up certain less-publicized facts related to disease risk of non-occupational exposures such as environmental or paraoccupational exposures, and also exposure to naturally occurring asbestos; it also underscores the difference in the age at onset, and sex distribution between mesotheliomas resulting from the occupational and non-occupational exposures. In this context, the chapter cites a study which attributes the risk of mesothelioma among women with so-called 'unknown asbestos exposure', to the past occupational exposure such as, doll manufacturing which was not considered as a potential exposure earlier. Mesotheliomas unrelated to asbestos exposure have also been pointed out in the chapter dealing with its molecular pathogenesis. Several case-control studies establishing the 'dose dependent' nature of the disease-risk with asbestos exposure and the evidence of progressively increasing risk with additional exposures are also highlighted; although no level of exposure is considered safe by any of the studies. With regard to mesothelioma mortality, an updated data from several studies with good statistical evaluation are presented, with one of latest studies citing an increased risk even after 40 years since the last exposure.

As stressed earlier, the rarity of this disease is a major constraint for any meaningful research, hindering the statistical power; mesothelioma being one such malignancy poses similar issues. Apparently, a network-based approach in such instances is a plausible solution. In the insert of the first chapter, the importance of an active network (national and international level), which would widen the research avenues with multi-institutional participation and the use of multi-modal therapeutic options involving both conventional and targeted approaches is highlighted.

The second chapter deals with the various imaging modalities for the detection and staging of MPM; it also addresses the role of imaging in monitoring of recurrent disease and the assessment of response to therapy. The limitations and relative advantages of different imaging techniques are highlighted, and the imaging findings of mesothelioma with each of these techniques are elaborated. While dealing with the

role of computed tomography (CT) in predicting the resectability of tumour, the need for rigid CT parameters in accurate diagnosis and staging of the disease are emphasized. The chapter also discusses the (*i*) ability of magnetic resonance imaging in distinguishing the histological subtypes of mesothelioma, based on the apparent diffusion coefficient; (*ii*) significance of contrast-enhanced CT and ^{18}fluorine-D-glucose integrated with positron emission tomography CT (F-FDG-PET/CT) in the monitoring of recurrent disease; and (*iii*) role of CT and ^{18}F-FDG-PET/CT in assessing the response to treatment using conventional size measurement criteria such as the WHO criteria, response evaluation criteria in solid tumours (RECIST) and modified RECIST (m-RECIST). Also discussed are the imaging features helpful in the differential diagnosis of mesothelioma vs. metastatic carcinomas, and the limitation of CT in the mesothelioma screening programmes.

The third chapter deals with surgical management of MPM, wherein the importance of biopsy obtained through pleuroscopy or video-assisted thoracoscopic surgery in distinguishing mesothelioma vs. metastatic carcinomas is emphasized as well as, in assessing the histological types of MPM. The relevant and essential details of the two major modalities of surgical management, the extrapleural pneumonectomy and, the radical or extended pleurectomy/decortication are provided, and their outcomes are compared. In the insert of this chapter, emphasis is laid upon the utility of debulking surgery in selected cases and a flow chart for surgical management of MPM is proposed.

The tissue diagnosis of MPM is most crucial for the clinical management of patients and most pathologists are aware of the complexities involved in mesothelioma diagnosis. The fourth chapter effectively addresses the pathological diagnostic aspects, including the molecular tests. The insert-chapter entitled, 'The Dark Side of Mesothelioma' quotes the recent guidelines from the International Mesothelioma Interest Group and the International Academy of Cytology that strongly support the possibility of diagnosing epithelioid and biphasic types of mesothelioma on cytological samples using smears and cell blocks in conjunction with immunostains. A substantial portion of the chapter is dedicated for diagnostic cytopathology of MPM. The role of ancillary studies is well addressed, discussing the practically relevant immunocyto/histochemical (ICC/IHC) panels, with a due emphasis on the new marker BRCA-associated protein-1 (BAP-1). A striking variation in the expression of desmin and epithelial membrane antigen between the normal/reactive mesothelial and malignant mesothelial cells is well brought out, along with a mention of certain new markers such as CD24 and GATA-binding protein factor-6 that are currently being tested to distinguish between mesothelioma and pulmonary adenocarcinoma. The utility of commercially available Urovysion kit for determining the ploidy by fluorescence-*in-situ*-hibridization (FISH) technique is stressed upon. MPM shows aneuploidy and homozygous deletion of 9p21 band, wherein p16 is localized. The 'histology' portion of the chapter includes the morphological/architectural descriptions and the practical relevance of the WHO histopathological types of mesothelioma. In this context, it is not only important to distinguish epithelioid mesothelioma from metastatic carcinoma, but also to differentiate the sarcomatoid and desmoplastic variants of mesothelioma from other spindle cell neoplasms and fibrous pleurisy (a benign non-neoplastic condition), respectively for effective patient management.

The fifth chapter gives an overview of the molecular biological aspects, briefly reviewing the pathways involved in the mesothelioma tumorigenesis. Emphasizing the role of 'yes associated protein (YAP)', a transcription co-activator of the Hippo pathway, the scope for developing specific drugs targeting the YAP-Hippo activity is suggested. The key role of beta-catenin in the Wnt pathway and the predictive/prognostic value of Wnt7A protein are highlighted. A heterogeneous role of the notch receptors (Notch pathway) in mesothelioma tumorigenesis and an overexpression of certain target genes of the Hedgehog pathway such as glioma-associated protein-1 and patched, and their association with worse prognosis are emphasized.

Of all the molecular events involved in mesothelioma tumorigenesis, the loss of tumour suppressor genes such as p16, p14, NF-2 and BAP-1 is considered the chief driver events. In this context, a sizable portion of the chapter is dedicated to addressing the practical utility of the combined analysis of p16 and BAP-1 in distinguishing reactive from malignant mesothelial proliferations in both cytological and histological samples. Citing a high sensitivity, but a lower specificity of these markers, the chapter points out at the limitation of these otherwise valuable markers for distinguishing benign vs. malignant mesothelial cells. The role of MTAP finds its first mention in the insert of the chapter, wherein its utility

with a concordance between MTAP analysis by IHC and 9p21 (CDKN2A gene) by FISH in cell blocks is emphasized; suggesting also, the utility of concomitant assessment of MTAP-1 and BAP-1 in differentiating benign vs. malignant mesothelial cells. Furthermore, highlighted in the chapter is the prognostic significance of 'loss of p16' as an independent risk factor.

The last two chapters address the current, as well as the futuristic strategies of MPM. Emphasizing the need for an experienced, multi-disciplinary team approach, the sixth chapter discusses the modifications in patient management depending on factors like the clinical-stage/operability, performance status, adequate cardiopulmonary function, and patient tolerance. Thus, multimodality therapy is intended for the cure and used in selected cases of stage I/II disease; whereas, an induction therapy followed by surgery is preferred in more advanced disease (for downstaging of tumour and to prevent distant relapse).

Chemotherapy being the choice of treatment in advanced disease, the chapter discusses the effectiveness of essential drugs used in MPM (either as a single agent or in combination) such as cisplatin, pemetrexed and doxorubicin/daunorubicin, along with the utility of adding modulating agents for reducing the drug toxicity. The futuristic strategy exploits the currently available research outcomes, with regard to molecular alterations, angiogenesis and immunotherapy.

Radiotherapy is said to have no well-defined role in MPM. However, the seventh chapter deals with its palliative role, as well as, its use as adjuvant therapy following radical surgery. On the whole, the book is informative and covers almost all aspects of MPM; although, in a brief but effective manner and thus, essentially could serve as a useful and handy guide for clinicians managing patients with MPM.

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