ELSEVIER

European Journal of Cancer 40 (2004) 1465–1466

European Journal of Cancer

www.ejconline.com

Editorial comment

Langerhans cell histiocytosis: portrait of a disease as a rare tumour

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Received 16 March 2004; received in revised form 17 March 2004; accepted 18 March 2004
Available online 25 May 2004

At first sight, defining tumours or groups of tumours by their incidence or prevalence-rarity, for example, seems counterintuitive, especially when they seem to have nothing in common from the medical, biological, pathophysiological or therapeutic point of view. Yet these patients' medical and psychosocial constraints and experiences may share a number of important features. The diagnostic procedure may be lengthy and difficult. Often, the histopathological findings are puzzling, not least for the pathologist. The patient is often left in the dark longer than usual, because his doctor only discovers the disease during the diagnostic process. In addition, the image that medical personnel have of the disease may be coloured by the ''last case seen in the department'', sometimes several years previously, with the attendant risk of outdated or otherwise inappropriate decisions. Despite goodwill and good sense, the referring physician may not have the time needed to analyse the patient's situation calmly, and being rare, the disease may have no agreed work-up or treatment strategy. Yet, it is now generally accepted that all treatments need strict assessment and validation, and treatments for rare diseases are no exception.

Rare tumours – usually defined as those with a prevalence below 5 per 10,000 – probably represent, overall, between 5% and 10% of all malignancies.

In this context, the work reported by Professor Arico both in this issue of the Journal, and also in a previous study [1], is exemplary.

Adult-onset Langerhans cell Histiocytosis (LCH) is a good example of a highly perplexing rare tumour. Patients present with an extremely wide variety of symptoms, reflecting the different types and degrees of organ involvement. This leads to the involvement of a broad range of specialists including orthopaedists, dermatologists, endocrinologists, pulmonologists, neurologists and hepatologists. Oncologists and internists are rarely consulted in the initial stages and, only if ''things go badly'', yet both can play a key co-ordinating role. The oncologist's pivotal position is explained by the fact that it is he who has the weapon – chemotherapy – needed to fight the disease. Yet not all oncologists realise the importance of their role in this setting. Why? The first reason is that Histiocytosis is not regarded as a ''conventional'' malignancy. Histopathologists may talk of Langerhans' cell ''accumulation'' or ''activation'' rather than ''proliferation'' – an important difference from true malignancy. Even studies of clonality may yield puzzling results; with some reports examining only one sample per patient and therefore showing evidence of LCH cell monoclonality in some forms of the disease [2] whilst others have reported polyclonality, when distinct lesions of the same patient have been studied at the same time [3,4]. Second, the natural history of this disease is atypical and often fluctuates. Some episodes of disease activity, such as isolated bone lesions, resolve without treatment, whilst others, such as the neurodegenerative syndrome associated with LCH, appear totally refractory to treatment, probably because they are long-established and cicatricial. The same applies to other severe sequelae such as sclerosing cholangitis or terminal respiratory failure, which can appear after years of apparent dormancy. The oncologist's role as ''pilot'' is nonetheless essential, if only to reassure those involved that there is a pilot on board... Professor Arico offers the pilot a roadmap for the management of LCH, based on a sound, methodical approach.

All concerned physicians, throughout the world, are invited to contribute to the collection of information on adult LCH, including the analysis of retrospective data. This approach needs consensus agreement on nosology and other definitions. In this paper, Professor Arico therefore first describes the wide clinical spectrum of adulthood-onset disease [1], before turning to

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0959-8049/$ - see front matter
doi:10.1016/j.ejca.2004.03.017

outstanding therapeutic questions. Readers may be surprised to learn that, despite nearly 50 years of availability, the potential value of cortico-steroid therapy for pulmonary involvement by LCH has not yet been determined and there has been no systematic study of smoking cessation. The same applies to vinblastine, which is the reference drug for childhood LCH [5,6] and has been available since the 1960s, with well-known short-term and long-term tolerability. Without this necessary groundwork, all clinical research, and even individual treatment choices, are simply based on personal instinct. Indeed, why use new treatments, such as cladribine (Leustat), biphosphonates or thalidomide, when most ''standard'' treatments have not yet been properly evaluated. Other drugs such as methotrexate, 6-mercapto-purine and cytosine arabinoside, for example, are also active in paediatric LCH, but this does not mean that these drugs should be used from the outset, or even that results in children can be directly extrapolated to adults. The simple fact that the disease is rare does not mean that treatments can be recommended without first estimating their likely risk–benefit ratio. Modern medicine, by definition, questions individual physicians' ''instinct'' or ''inspiration'', placing greater confidence than before in the ability of scientific analysis to identify the most explicit, safest and most solidly documented treatments. Without a reference point, there can be no measurable or validated improvement. This is why Professor Arico's approach is so crucial and so laudable, and why it is exemplary as regards our approach to other rare tumours. Much can be learnt from rare diseases. LCH, for example, is practically the only known human disease of dendritic cells, whose key immunological role, especially in cancer surveillance, is now of considerable interest. The importance of a methodical approach is that it may not only throw light on a disease process, but also on the physiological function of the normal cell counterpart. That is already the case in LCH research in that in the Histiocyte Society and the Nikolas Symposium, both of them deeply involved in the ''quest for the Holy Grail'', the aetiology and pathobiology of LCH, are now closely linked to basic scientists in the Histiocyte and Dendritic cell fields and mutual benefit is already evident [7].

Acknowledgements

The author thanks David Young for linguistic revision of the text.

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