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ITEM CLASSIFICATION AND GRADING: AN APPROACH TO NON-MATHEMATICAL MORPHOMETRY

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ABSTRACT

Introduction to the theoretical backgrounds of item classification and grading is given. The approach is illustrated by three examples. These demonstrate the applicability of this type of investigation in the analysis of lymph node and spleen reactions in cancer patients, and in the analysis of changes in the thymus in experimental animals receiving specific immunosuppression. The need for an appropriate control material is emphasized. Item classification and grading is an alternative to more mathematical morphometry, and should be considered in situations in which more objective methods are too laborious.

INTRODUCTION

Classification and grading is very basic in the nature of diagnostic histopathology. Diagnostic histopathology itself originated from the results of early histopathologists who showed that there was variation in the microscopic appearance of disease processes affecting human tissues. In the diagnostic situation the pathologist looks at the section in the microscope and then tries to locate the lesion within the spectrum of disease processes available to him. In many respects this process is subjective and intuitive, and pathologists vary in how they call and classify the same lesions (Collan, 1982).

It is not always difficult to locate the cause of this variation. Diagnostic histopathology is very much an art, not a science. The whole process seems to be based on what we can

call experience gained by the pathologist in reporting slides. Sooner or later after looking at the slide he feels that he is ready to call the lesion with a definite diagnosis. If this proves difficult he usually turns to textbooks and articles written on histopathology of similar or related lesions, to find helpful clues for classification. In fact these clues are those used by former researchers in classifying lesions. Frequently, however, the help given to the pathologist is obscure and not detailed. We mention a few examples. Terms like atypia, dysplasia and pleomorphism are used very loosely. Atypia may be nuclear, cytological, architectural and even within corresponding entities, considerably varying in nature.

It is also surprising that in many contexts different morphological entities are combined but no rules of how this should be done are given. A good example is grading dysplasia of the uterine cervix. The latest recommendation in this field is that when condylomatous lesions (caused by papillomavirus) are present, standard classification into the 3 grades of dysplasia should be practiced. The dysplasias, however, are defined in a subjective fashion with little emphasis on the superficial atypia, which various pathologists will weigh differently. More definite rules about how to proceed shoud be necessary in contexts like this if benefits are to the expected (see e.g. Syrjänen, 1980b).

Against this background it is not suprising that many pathologists have tried to analyse the findings a bit further. This is especially true in research efforts which aim at quantifying the changes taken place. In this process the features seen on the specimen are listed and each feature defined. Usually, anatomical entities (subunits of the tissue) are the listed features. The division of tissue into subunits may proceed to a very detailed analysis of the subunits present. The process usually is stopped at a level considered appropriate for the study in question. The point here is that at the end of this process we no longer look only at the section as a whole but can concentrate on subunits composed of simply defined morphological structures. These structures can now be graded. Or changes (of whatever kind) can be graded. Usually 5 grades or less are used. There is, however, no reason why one could not apply a greater number of grades, but it is extremely important that each grade can be described clearly, and that there is a minimum of overlap between the grades used. This is to ensure the reproducibility of the grading.

PRACTICAL APPLICATIONS

The next few examples are intended to demonstrate how such an approach to non-mathematical morphometry using item

TABLE 1. LYMPH NODE MORPHOLOGY

	---	--	-N+	++	+++
Lymph node					
Size					
Architecture					
Altered diffusely					
Altered focally					
Cortical area					
Size					
Lymphocyte content					
Lymphocyte follicles					
Number					
Size					
Germinal centers					
Number					
Size					
Content of large lymphocytes					
Relative number of mitotic figures					
Relative number of macrophages					
Paracortical area					
Size					
Content of small lymphocytes					
Content of medium-sized lymphocytes					
Content of large lymphocytes					
Content of histiocytes					
Mitotic activity					
Medulla					
Size					
Medullary cords					
Width					
Content of large lymphocytes					
Content of plasma cells					
Content of small lymphocytes					
Sinuses					
Width					
Content of large lymphocytes					
Content of small lymphocytes					
Content of histiocytes					

N: Normal. One, two or three plus and minus signs indicate slight, moderate or marked deviation above or below the normal range.

classification and grading has been successfully applied in assessing the dynamics of lymphatic tissue reactions due to a variety of stimuli. In 1973, Cottier et al. introduced the standardized system of reporting human lymph node morphology

related to immunological functions (Cottier et al., 1973). This system is based on separate analysis of the different anatomical regions (subunits) of the lymph node, and grading of the parameters into 5 grades (Table 1). By so doing, the pathologist gets an impression on the reactivity of the thymus-dependent (T-region, paracortex) elements responsible for the cell-mediated immunity as well as of the bone-marrow-dependent elements (B-region, cortex, GC:s, medulla) mediating the humoral immune response. Also the sinuses with their histiocytes, contributing to the assisting function (macrophages) in immune reactions are graded. This system has been successfully applied on analysis of the reactions of lymph nodes draining a variety of human and experimental tumors (Syrjänen 1979, Syrjänen 1982). In this context, the necessity of an appropriate control series of lymph nodes from age- and sex-matched non-cancer patients should be emphasized (Syrjänen 1979, Syrjänen 1982). The results have shown that both the elements of humoral and cell-mediated immunity are severely impaired in the lymph nodes draining cancer (Syrjänen 1979, Syrjänen 1982) much more frequently than in those of healthy controls.

Another lymphatic organ with a number of important functions is the spleen. Also within the spleen white pulp, definite regions for T-and B-lymphocytes can be differentiated, and their structure can be subjected to grading analogous to the one described for the lymph nodes (Table 2). The cells responsible for humoral immune reactions are found in the peripheral periarteriolar lymphatic sheath (P-PALS) and in germinal centers (GC), whereas the T-cells are homed within the central periarteriolar lymphatic sheath (C-PALS). This system has been adopted on analyses of the spleen white pulp reactions in patients dying of a variety of malignant tumors (Syrjänen 1980a, Syrjänen 1982). Here again, the paramount importance of an adequate control material from age- and sex-matched control patients dying of courses unrelated to malignancy is emphasized (Syrjänen 1980a). The results obtained were analogous to those found in the lymph nodes, suggesting that also the spleen white pulp is subject to changes due to the general immunosuppression found at the terminal stage of malignancies (Syrjänen 1980a, Syrjänen 1982).

The third example of this kind of an approach comes from the field of experimental pathology, and deals with an analysis of thymic morphology in DBA 2 mice. In the thymus, too, different anatomical regions (subunits) can be differentiated on the basis of their separate functional activity as well as on different structural elements (Table 3). Thus, in the cortical area, immature thymocytes undergo a sequence of vigorous proliferations through which the mature thymocytes are formed from the stem cells committed to T-lymphocytes. The mature thymocytes move towards the medulla, where they leave the gland via the venules at the corticomedullary junction.

TABLE 2. SPLEEN MORPHOLOGY

	---	--	-N+	++	+++
Spleen					
Size					
Architecture					
Altered diffusely					
Altered focally					
Central periarteriolar lymphoid sheath					
Size					
Content of small lymphocytes					
Content of medium-sized lymphocytes					
Content of large lymphocytes					
Content of histiocytes					
Mitotic activity					
Peripheral periarteriolar lymphoid sheath					
Size					
Content of small lymphocytes					
Content of large lymphocytes					
Content of histiocytes					
Content of plasma cells					
Mitotic activity					
Germinal centers					
Number					
Size					
Content of large lymphocytes					
Content of macrophages					
Mitotic activity					

N: Normal. One, two or three plus and minus signs indicate slight, moderate or marked deviation above or below the normal range.

The dynamics of this process can be analysed by inducting a depletion of the thymic cells and following-up their recovery. This can be done selectively by antisera against the mature (theta-antigen positive) thymocytes or with antisera against the whole thymus gland (Syrjänen 1978). The effects of these two antisera seemed to be completely different, and their depletory effects on thymic cell populations could be easily analysed using the system outlined in Table 3 (Syrjänen 1978). Once again, an adequate control material is necessary also in such experimental designs, as repeatedly emphasized (Syrjänen, 1978, 1979, 1980a,1982).

The aim of the above examples was by no means to suggest that the lymphatic tissue is the only field where item classification and grading has its applications. Virtually all the organs and systems are approachable by this means, which

TABLE 3. THYMUS MORPHOLOGY

	---	--	-N+	++	+++
Thymus					
Size					
Architecture					
Altered diffusely					
Altered focally					
Cortical area					
Size					
Content of large lymphocytes					
Content of medium-sized lymphocytes					
Content of small lymphocytes					
Content of reticulum cells					
Mitotic activity					
Medullary area					
Size					
Content of large lymphocytes					
Content of medium-sized lymphocytes					
Content of small lymphocytes					
Content of reticulum cells					

N: Normal. One, two and three plus or minus signs indicate slight, moderate or marked deviation above or below the normal range.

on special occasions might well be an alternative to mathematical morphometry. This is especially true, if large series of specimens are to be analysed, but of course the selection of the method depends on the current problems to be handled with. As we will see later during this symposium, the present kind of approach gives results fully comparable to those of direct quantitative measurements in hands of experienced pathologists.

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