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Virchows Archiv A

Letter to the editor

Comments on the paper by Krech and Thiele

"Histopathology of the bone marrow in toxic myelopathy. A study of drug induced lesions in 57 patients"

Sirs. Acquired aplastic anaemia (AA) has been associated with exposure to drugs for many years, and for a few substances, epidemiological data and in vitro studies suggest an aetiological relationship (Heit and Heimpel 1980). A major problem is the lack of variables suited to link drug exposure to AA in an individual patient. In a recent paper in this journal, Krech and Thiele (1985) stated that histopathological changes in the bone marrow may be used as evidence of a "toxic myelopathy". I have, however, serious doubts that this conclusion is supported by their data.

The authors analysed retrospectively 69 trephine biopsies from hospitals affiliated with the University of Hannover, obtained within a $5^1/_2$ year period from patients with bi- or pancytopenia. Twelve cases were excluded for the presence of "inflammatory disease". By analysis of the files, drug associations were found in all of the remaining 57 cases and these data were interpreted as evidence of the toxic nature of the myelopathy. Apparently, the prediagnostic period of potential exposure was not defined. In Table 1, each case was attributed to one drug regarded as toxic inducer. Simple arithmetics would give a total of 63 instead of 57 cases from the second column. The drugs mentioned include a majority of those which have been previously accused as potentially responsible for AA, but there are also substances which have been accused of inducing agranulocytosis but not AA. Classification of all cases as "drug-induced" is a striking contrast to the pertinent literature, which classifies between 20% and 80% as related to drugs. Allocation of a given case to the group of drug-induced AA may often be biased by correct or erroneous a priori evidence, and the fraction of truly drug-induced aplastic anemias is probably lower than previously accepted.

Table 2 of the paper shows that the material studied does not correspond to an accepted disease entity as AA, but includes ill-defined pancytopenias with normo- or hypoplastic bone marrow. Figure 3b shows hyper-rather than hypocellularity as stated in the legend, and the micromegakaryocytes described could be regarded as evidence of preleukemic myelodysplasia. Figures 2b and 3c show an essentially normal bone marrow.

There are no controls, neither for drug exposure nor for non-toxic bone marrow failure. Such controls would be the minimal requirement to support the authors' hypothesis, that the histopathological changes they believe to see are evidence of toxic damage to the bone marrow.

References

Heit W, Heimpel H (1980) Drug-induced aplastic anaemia: Clinical aspects. Clin Haematol 9:641–662

Krech R, Thiele H (1985) Histopathology of the bone marrow in toxic myelopathy. A study of drug induced lesions in 57 patients. Virchows Arch [Pathol Anat] 405:225–235

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Virchows Arch [Pathol Anat] (1986) 408:447

Virchows Archiv A

The authors reply as follows:

Sir. The aim of this study was to provide morphological aspects of the bone marrow following drug ingestion, i.e. toxic myelopathy with emphasis on the evaluation of plastic embedded trephine biopsies. Consequently a semiquantitative evaluation of our results summarized in Table 2a encompasses very disparate features ranging form aplasia to normo- and hyperplasia and thus only partially corresponds with the clinical entity "acquired aplastic anaemia (AA)". This discrepancy may be explained in some patients by the time of performance of the trephine biopsy (aplastic or regeneratory phase), a focal pattern of bone marrow lesion or a special drug effect (agranulocytosis or panmyelopathy).

Figure 3b shows a prominent interstitial oedema and, as marked by arrow heads, several micromegakaryocytes. The overall cellularity is decreased, when considering the given age of this patient (12-year-old boy), i.e. there is hypoplasia. Micromegakaryocytes of an atypical appearance are frequently encountered in preleukaemic stages, however, in this context and without gross abnormalities they are suggestive for regeneratory changes. Figures 2b and 3c certainly do not display a normal bone marrow (as illustrated in Fig. 1a, but interstitial oedema and perivascular plasmacytosis in Fig. 2b (compare with inset Fig. 1c) or in Fig. 3c a focal proliferation particularly of the erythropoiesis in an elderly patient (regeneratory phase).

The authors are fully aware of the difficulties to allocate certain drugs to a given lesion of the bone marrow. For this reason 5 patients as controls are explicitly mentioned, in whom an improvement of pancytopenia was observed shortly after cessation of drug therapy. In addition the mode of selection of our 57 patients was carefully described and the 12 cases with an underlying "inflammatory disease" excluded to avoid a confusion of bone marrow changes seen in hepatitis (hepatotoxic myelopathy) or rheumatoid condition (hyperergic myelitis) with a possible drug-related effect.

Table 1 may indeed be a matter of misunderstanding. The apparent discrepancies between the number of patients and the drugs mentioned can be easily explained by repeated listing. For example there were a few patients with documented intake of several drugs which have been reported to have a toxic effect on the bone marrow.

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