ABSTRACT

Macrophage activation and secondary hemophagocytic syndrome are rarely reported in association with Langerhans cell histiocytosis (LCH). The authors reviewed their pathology files for cases of LCH in which evidence of macrophage activation coexisted and report 30 such cases indicating that the association is not that rare and may even be underdiagnosed unless specifically sought. Available clinical data were collected and correlated with pathological findings. Of the 30 cases of LCH with varying degrees of macrophage activation, 29 had multisystem disease. The cases were graded from I to V on the basis of evidence for, and severity of, macrophage activation; cases in category I had evidence of fully developed hemophagocytic syndrome whereas those in category V had limited evidence of macrophage activation. There were seven cases with fully developed hemophagocytic syndrome (category I) and an additional five with hemophagocytosis and some but not all of the features of hemophagocytic syndrome (category II). Most of these 12 cases were young children with high-risk LCH and poor prognosis; 4 are known to have died. Coexisting hemophagocytic syndrome in these cases of LCH may have contributed to their poor prognosis. The association of LCH with macrophage activation, though more than coincidental, is of unknown pathogenesis, but the role of T lymphocytes and cytokines is prominent in both disorders and is presumed to link the two.

Key words: histiocytosis, Langerhans cell histiocytosis, hemophagocytic syndrome, pediatric

INTRODUCTION

Langerhans cell histiocytosis (LCH) and the hemophagocytic syndrome are categorized separately in a contemporary classification of histiocytic diseases; however, the coexistence of LCH
and secondary hemophagocytic syndrome is acknowledged in that treatise [1]. Our report concerns this association in 30 cases, 12 of which had fully developed or partial hemophagocytic syndrome.

LCH, the primary disorder in this scenario, is a monoclonal process characterized by lesional histiocytes with a phenotype of an activated dendritic cell akin to that of the Langerhans cell, the prototypical antigen presenting cell, [2,3]. LCH is diagnosed definitively by biopsy and morphological assessment. The hemophagocytic syndrome, the secondary process in this association, is considered to reflect poorly controlled activation of macrophages with predominantly antigen-processing functions and is, in contrast to LCH, defined by clinical and clinical laboratory parameters, with a limited role of morphological methods [4,5]. T lymphocytes and cytokines seem to play a prominent role in both disorders [6–12].

Activation of macrophages and lymphocytes is the pivotal process that varies in degree but, when severe, is expressed as the hemophagocytic syndrome [4,5]. Reflections of macrophage activation may occasionally be so prominent in patients with LCH that the diagnostic signs of LCH, the primary disorder, are obscured and management is complicated. Our experience with 30 cases of LCH with varying degrees of macrophage activation, including some with fully developed secondary hemophagocytic syndrome, suggests that the coexistence of the two disorders is more than coincidental and is clinically important. Young children, at risk for a more severe clinical course of LCH, are also likely to have the most prominent macrophage activation when the disorders coexist.

METHODS

The material came from the pathology consultation files of B.E.F. and R.J. In five cases, consultation was requested to verify a diagnosis of primary hemophagocytic syndrome. In others, assistance was sought to verify a diagnosis of LCH, to make a diagnosis when an unspecified histiocytic disorder was suspected, or to define the extent of disease in LCH. Clinicians involved with the case were contacted for additional clinical and follow-up information, but the response rate was low.

Ten cases, included here, have been reported in the context of the hepatic pathology of histiocytic disorders and four were featured in a report on lymph nodes in histiocytosis [13,14]. Material from these 14 cases was re-examined and categorized as noted below.

Hematoxylin and eosin (H&E)—stained sections were available for all cases and one or more sections stained for CD1a were available in many. A definitive diagnosis of LCH was established in all cases by published criteria [1]. Cases were stratified as single-system or multisystem disease as in the LCH 1 treatment protocol [15]. We equate CD1a− histiocytes with macrophages in the context of this report.

Morphological features that reflect activation of histiocytes are (1) hemophagocytosis by histiocytes [4,5], (2) prominent and enlarged von Kupffer cells of liver [13] (3) S-100+ macrophages [3] (4) coarsely vacuolar and granular CD68 positivity, and (5) increased expression of MHC class II molecules and macrophage colony-stimulating factor (M-CSF) receptors on histiocytes [16]. We considered only the first two features because of limitations of material available to us. This histopathology is illustrated in Figure 1. The 30 cases of LCH were separated into five categories to reflect the amount of clinical and morphological evidence of macrophage activation. Cases in categories with the lower numbers had the strongest evidence or the most manifestations of macrophage activation.

Category I included cases with fully developed hemophagocytic syndrome as defined previously [4]. Briefly, these patients had hemophagocytosis and all of the following features simultaneously: fever of noninfectious source, hepatosplenomegaly, cytopenias, hypofibrinogenemia, and hypertriglyceridemia. Category II consisted of cases with hemophagocytosis and at least two, but not all, of the features noted in category I. Category III included cases showing hemophagocytosis in any tissue and signs of macrophage activation in liver biopsies as described previously—i.e., prominent numbers of enlarged von Kupffer cells, often occurring with faint S-100+ cytoplasmic staining [13]. Category IV included cases showing only conspicuous hemophagocytosis in the bone marrow, liver, or lymph node, but no other signs of macrophage activation. Category V, consisted of cases in