THE RELATIONSHIP BETWEEN EOSINOPHIL AND HODGKIN CELL DENSITIES IN LYMPH NODES OF CHILDREN WITH DIFFERENT SUBTYPES OF CLASSICAL HODGKIN'S DISEASE

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Abstract- Although eosinophils are frequently found in lymphatic tissues of patients with classic Hodgkin's disease (HD), no substantial data reveals the relationship between tissue cellular densities of eosinophils and Hodgkin-Reed-Sternberg cells in involved lymph nodes. In this study, we determined the respective cellular densities of these cells on lymph node tissue sections of 80 pediatric patients with different subtypes of classical HD from 1992 to 2002. The mixed cellularity (MC) and lymphocyte-rich (LR) subtypes displayed the maximal (67.50%) and minimal (2.50%) percentages of total number of cases. Also the nodular sclerosis (NS) and lymphocyte depletion (LD) subtypes composed 26.25% and 3.75% of the cases, respectively. LR and LD subtypes were omitted from correlation studies, owing to their respective suboptimal number of cases and unreliability of statistical results. Eosinophil and Hodgkin cell densities were determined by cell counting on histological slides of two other subtypes (75 patients), separately. The NS subtype revealed a strong positive correlation ($r = +0.9$) and nearly a linear relationship between two density values. Also, a poor correlation ($r = -0.3$) was detected between two densities in MC subtype. Considering different signal transduction pathways in subtypes of classical HD, it was postulated that the proposed correlation of tissue eosinophilia with poor prognosis in NS is probably related to their role in protection of tumoral Hodgkin cells from apoptosis and subsequent increase of their tissue concentration, a process that is not observed in MC subtype with some other complicating molecular factors.

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Key Words: Hodgkin's disease, histopathologic subtypes, Hodgkin cell, tissue eosinophilia

INTRODUCTION

Early descriptions of the natural history of patients with Hodgkin's disease (HD) showed a disease with a highly variable clinical course, which prompted and continued to prompt numerous clinical studies designed to identify new prognostic factors or improve already established prognostic factors. According to the recently performed epidemiological studies in Asia, HD comprises about 33% of the total number of lymphoma patients in Iran (1, 2). There is also marked presentation of this type of lymphoma in children. In recent decades, many investigations have revealed the importance of some of the histopathological features in prognosis of various subtypes of HD (3-7). However, only a few of them have examined these prognostic determinants in the pediatric age group.

In recent years, an important issue in HD has been the interrelations among tumor cells and different types of inflammatory cells in tissue sections obtained by biopsy. It has been revealed that cellular composition in tumoral tissue is the consequence of different cytokines and chemical

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mediators, released from neoplastic and inflammatory cells. Having previously shown that the "concentration" of the Hodgkin-Reed-SterSternberg (HRS) cells in the involved lymph node tissue is an important prognostic factor in early stages of HD (8), and considering the result of recent investigations that tissue eosinophilia correlates strongly with poor prognosis in some types of HD (9), theoretically, it seems likely that a correlation might be existing between tissue densities of neoplastic HRS cells and eosinophilic granulocytes, at least in some of the subtypes of classical HD. We stress on "classical" because CD30 antigen (a member of the tumor necrosis factor receptor superfamily) that has the capability of binding to CD30 ligand on eosinophilic cells and inducing an apoptosis-protection signal in tumoral HRS cells, is fully expressed only in classical type of HD (10,11). Owing to this significant difference between classical and lymphocyte predominance HD, the latter has been omitted from this study, although its occurrence in pediatric age group is considerable. Furthermore, all the cases reviewed in this study have had a confirmed diagnosis of classical HD, to prevent from possible effects of any unpredictable or unrecognized determinant factor.

MATERIALS AND METHODS

In this investigation, the population of the study consists of all histologic slides made from stored paraffin blocks of the lymphoid tissue specimens, obtained from lymph node biopsy of up to 15-year-old patients with one of the histopathologic subtypes of HD in Hazrat-e-Ali Asghar Children Hospital. Having in mind that this observation is limited to a certain period of time, the samples of the study were selected non-randomly and by convenient route. According to this specification, a total number of 80 cases were selected for the study. This investigation is an observational study with descriptive, cross-sectional approach, undertaken for exploring any correlation between two measurable histopathological variables (eosinophil and Hodgkin cell densities in histologic slides prepared from the lymph node tissue sections of pediatric patients with each subtype of classical HD).The individual cases were selected from anatomic pathology patient registry books, based on known factors mentioned above. Then the related paraffin blocks were collected from surgical pathology file archive. Owing to the poor preservation of a few long-stored blocks, they were omitted from the study.

All of the paraffin blocks were prepared for sectioning. From each lymph node tissue block, four serial sections were cut at a micrometer setting of 3 mm, and mounted on two microscopic slides. The slides were stained with standard hematoxylin & eosin staining method. The sections were examined under a microscope with a 40x objective and 10x eyepiece (total magnification 400x). All histopathological slides were reviewed according to new proposed WHO classification system for confirming the previous pathologic diagnoses. The respective slides of the nodular lymphocyte predominance HD were excluded. A total number of 80 cases in classical HD category (sample of the study) were considered for further evaluation. They included: lymphocyte-rich HD (2 cases), nodular sclerosis HD (21 cases), mixed cellularity HD (54 cases) and lymphocyte depletion HD (3 cases). Owing to the suboptimal number of cases in lymphocyte-rich classical and lymphocyte depletion HD subtypes, and unreliability of the correlation analytic results for very small samples, their corresponding histologic sections were omitted from the study. Finally, the histologic slides of 75 cases with classical HD diagnosis (21 cases of nodular sclerosis and 54 cases of mixed cellularity) were prepared for further evaluation.

Ten randomly selected, representative high-power fields (HPF) were investigated. First, the total number of cells within each particular HPF was determined. In a second step, eosinophils and Hodgkin cells within the same HPF were separately counted and the approximate percentages of them were calculated. A representative field for counting 10 HPF was defined as an area with a high tumor cell density in a field typical of HD but without fibrosis or necrosis. For recording and verification of investigational results for subsequent analysis, a special checklist form was designed. This checklist encompasses a case order number, a pathologic code

number compatible with the pathologic registration number for each case in the study, age of the pediatric patient, the respective percentages of Hodgkin and eosinophil cell densities in each of 10 high power fields in related histologic sections, and total sum of these numerical values.

The statistical method for examination of the obtained results in this study is correlation analysis with determination of simple correlation coefficient or Pearson's product-moment correlation coefficient. This method is suitable for determining the mutual correspondence between two cellular densities in different subtypes of HD (12). Also, the respective scatter diagrams are plotted and the least squares line is drawn for evaluation of deviations from the mean. The study is compatible with medical ethics. All of the histological slides are labeled with special pathologic code numbers rather than the name of the patients, and there is no inconsistency with moral principles in presentation routs or interpretation of results.

RESULTS

The frequency chart of different subtypes of classical HD in pediatric patients is presented in figure 1. According to this study, the mixed cellularity subtype displays maximal percentage of the total number of cases (67.50%), and the lymphocyte rich subtype displays minimal number of them (2.50%). Also, the nodular sclerosis and lymphocyte depletion subtypes compose 26.25% and 3.75% of the classical HD, respectively.

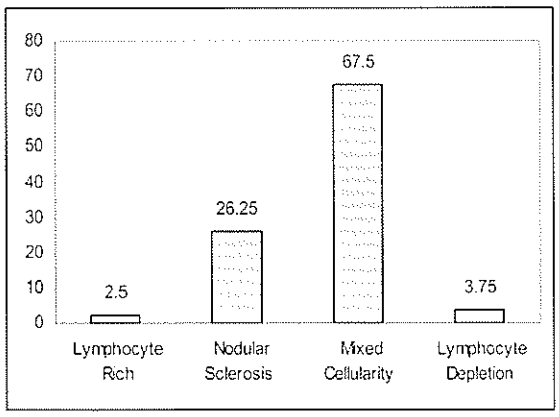

Fig. 1. Relative frequency of different subtypes of classical Hodgkin's disease in our pediatric patients.

Using the results of tissue cell counting and obtained eosinophil and Hodgkin cell densities in nodular sclerosis and mixed cellularity subtypes of HD, the correlation coefficients between eosinophil and Hodgkin cell densities were calculated +0.9 (for nodular sclerosis subtype) and -0.3 (for mixed cellularity subtype), and respective diagrams were plotted (Figures 2-4).

Figure 1 shows the scatter diagram with plotting the obtained data for cellular percentages of eosinophil and Hodgkin cells in cases of nodular sclerosis classical HD, with two axes drawn through the mean point. The distances of the points from these axes represent the deviations from the mean.

In the top right section of figure 2, the deviations from the mean of both variables are positive. Hence, their products will be positive. In the bottom left section, the deviations from the mean of the two variables will both be negative. Again, their product will be positive. In the top left section of figure 2, the deviations of Hodgkin cell percentage from its mean will be positive, and the deviation of

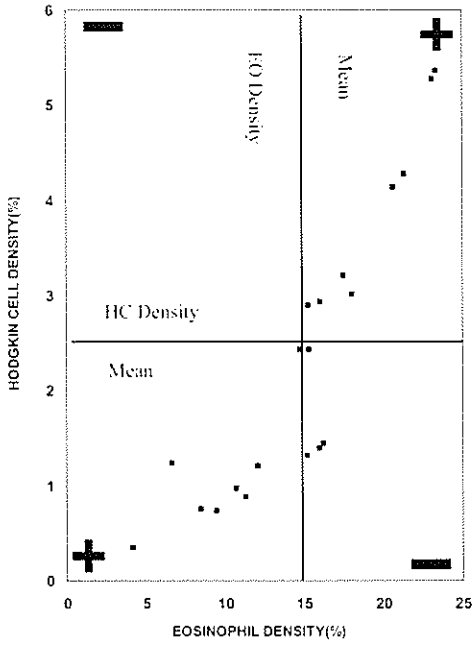

Fig. 2. Scattergram with axes through the mean point revealing a positive correlation between eosinophil (EO) and Hodgkin cell (HC) densities in 21 cases of nodular sclerosis classical Hodgkin's disease.

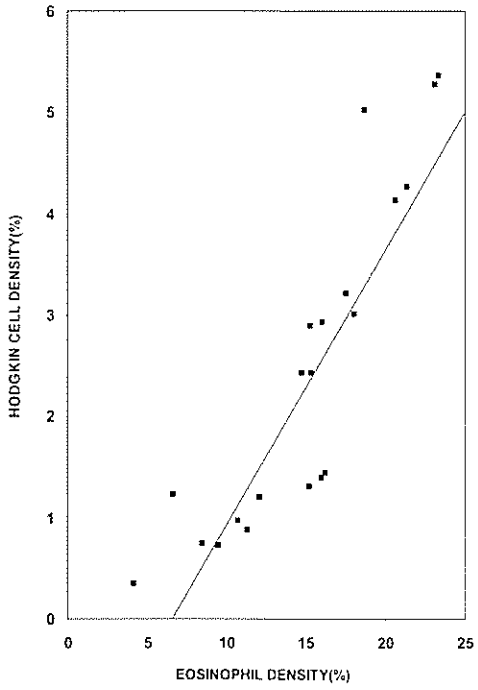

Fig. 3. The least squares line, drawn on the scattergram, represents the relationship between eosinophil and Hodgkin cell densities and their deviations from this line in 21 cases of nodular sclerosis classical Hodgkin's disease.

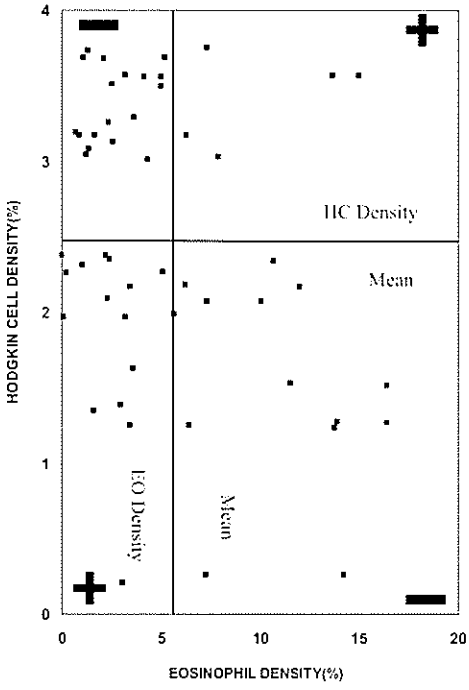

Fig. 4. Scattergram with axes through the mean point revealing no correlation between eosinophil (EO) and Hodgkin cell (HC) densities in 54 cases of mixed cellularity classical Hodgkin's disease.

eosinophil percentage from its mean will be negative.

The product of these will be negative. In the bottom right section, the deviations from the mean of the two variables will both be positive. Again, their product will be negative. In figure 2, almost all the values are scattered in top right and bottom left sections. So, nearly all these products will be positive and their sum will be positive.

Inspection of figure 2 reveals that nearly all of the points are scattered along a presumed line. Hence it may be possible to draw the least squares line which best represents the relationship between eosinophil and Hodgkin cells percentages. This will be achieved by making the sum of squares of the deviations about the line a minimum (Figure 3). Figure 4 shows the scatter diagram with plotting the obtained data for cellular percentages of eosinophil and Hodgkin cells in cases of mixed cellularity classical HD, with two axes drawn through the mean point.

The distances of the points from these axes represent the deviations from the mean. In the top right section of figure 4, the deviations from the mean of both variables are positive. Hence, their products will be positive. In the bottom left section, the deviations from the mean of the two variables will both be negative. Again, their product will be positive.

In the top left section of figure 4, the deviations of Hodgkin cell percentage from its mean will be positive and the deviation of eosinophil percentage from its mean will be negative. The product of these will be negative. In the bottom right section, the deviations from the mean of the two variables will both be positive. Again, their product will be negative. In figure 4, nearly the same number of points are scattered in each of the sections of top left, bottom right, and bottom left, and a fewer points are seen in top right section. So, there are nearly as many positive as negative products and the sum is closer to zero than the sums in figure 2.

DISCUSSION

According to the frequency chart (Figure 1), the mixed cellularity subtype comprises the highest number of cases among the different subtypes of classical HD in pediatric patients studied, and nodular sclerosis, lymphocyte depletion, and lymphocyte-rich subtypes compose the remainder, in descending order of frequency.

The correlation coefficient statistically calculated for nodular sclerosis subtype is very close to +1 (+0.9), indicating a high correlation between eosinophil and Hodgkin cell tissue densities in this subtype, whereas this coefficient for mixed cellularity subtype is closer to zero than to -1 or to +1 (-3), indicating a poor correlation between eosinophil and Hodgkin cell tissue densities. The scattergram plotted for nodular sclerosis subtype (figure 2) reveals that nearly all the products of deviations from the mean of the two variables and their sum are positive, hence, there is a positive correlation between eosinophil and Hodgkin cell densities; as one increases so does the other. Furthermore, the special distribution of variables in figure 2 gives us the possibility to draw a straight line on scattergram (Figure 3). This line, "the least squares line", elucidates the relationship between variables and their deviations from this line. The scattergram plotted for mixed cellularity subtype (Figure 4) reveals that there are nearly as many positive as negative products of deviations from the mean of the two variables, and the sum is closer to zero than the sums in figure 2. Also, it is impossible to consider a straight line for elucidating the linear relationship of the variables on scattergram.

These results present a reliable evidence that tissue densities of eosinophils and Hodgkin cells are positively correlated in nodular sclerosis subtype of HD and not in mixed cellularity subtype. By consideration of this fact that tissue Hodgkin cell concentration is an important prognostic factor in all subtypes of HD, and having in mind that tissue density of eusinophils correlates strongly with poor prognosis in only nodular sclerosis HD (3-7, 9, 13-19) it is postulated that the poor prognostic role of eosinophils in nodular sclerosis subtype is mediated through their effects on concentration of Hodgkin cells.

It has been revealed that cellular composition in tumoral tissue is the consequence of different cytokines and chemical mediators, released from neoplastic and inflammatory cells (20-32). These cytokines can activate or inhibit a certain type of cytoplasmic or nuclear receptors and transduce a specific signal that may result in enhance neoplastic proliferation or induce apoptosis and cellular death. One of these interactions is between the inflammatory cell cytokines (*e.g.*, CD30 ligand) and TNF receptor superfamily members such as CD30, CD40 or TNFR1, expressed on HRS cells of "classical" HD (33-40). Among these receptors, the expression of CD30 molecule can be induced on normal peripheral blood band T cells by mitogens and viruses such as EBV and HTLVI and II. The ability of CD30 to interact with various members of the TRAF family of signal transduction molecules in Hodgkin cells may result in a complex cascade of signaling events in HD. One of the important cellular sources of functionally active CD30 ligand for Hodgkin cells is eosinophilic granulocyte (41-43). These cells may be attracted by several factors including platelet activating factor, RANTES, IL-16, MCP3, MCP4, MPIF-1 and 2, eotaxin and IL-5, many of them are synthesized and secreted by Hodgkin cells (13). In fact, the Hodgkin cells own recruit the eosinophils to neoplastic lymphoid tissue and then, these granulocytes by releasing inflammatory cytokines such as CD30 ligand can mediate their effects through interaction with TNF receptor superfamily members on Hodgkin cells. CD30 engagement by CD30L-expressing eosinophils results in activation of predominantly TRAF-2-induced NFKB and a dose-dependent proliferation of Hodgkin cells as well as antiapoptotic signals in these cells. In nodular sclerosis subtype, the expression of some of the eosinophil attracting factors (*e.g.*, eotaxins) is much higher than in mixed cellularity subtype; this may have a profound impact on recruiting of more eosinophils to neoplastic tissue (40, 44). Furthermore, we remember that in mixed cellularity HD, a subtype that is much more often associated with an EBV infection than nodular sclerosis (40, 45, 46), the latent membrane protein 1 of EBV (a signaling homolog of the TNFR superfamily

expressed in HRS cells) serves as a potent activator of transcription factor NFKB (antiapoptotic effect on tumor cells), and as an important inducer of interferon-γ-inducible protein-10 (IP-10) expression (apoptotic effect due to known antitumor properties of IP-10 (9, 13). It seems that resistance to apoptosis resulting from CD30-CD30L interaction between Hodgkin cells and eosinonphils in mixed cellularity subtype is complicated with both antiapoptotic effect of LMP1 protein on HRS cells and antitumoral effects of IP-10 and some related cytokines. Therefore, the dysregulation of genes controlling proliferation and prevention from apoptosis in mixed cellularity HD are caused by both EBV infection and eosinophils.

This might explain why in mixed cellularity cases no positive correlation was observed between eosinophil and Hodgkin cell tissue densities in this study. Indeed, the complicating effect of EBV infection on transduction signaling pathways has been "omitted" in nodular sclerosis HD and this may allow a linear relationship between eosinophil and Hodgkin cell densities in this subtype.

Hence, we hypothesize that the proposed correlation of tissue eosinophilia with poor prognosis in nodular sclerosis HD is related to effective role of eosinophilia in protection of Hodgkin cells from apoptosis and subsequent increase of their tissue concentration.

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