Changes in IL-1, IL-1 Receptors and IL-1 Receptor Antagonist in Recently Diagnosed Lymphoma and Their Implication in Systemic Symptoms

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Abstract

Interleukin -1β (IL-1β) and its modulating agents, IL-1 receptor antagonist (IL-1Ra) and IL-1 soluble receptor type II (IL-sRII) were assessed in sera of previously untreated 50 patients suffering from lymphoma. They were 30 males and 20 females with mean age 37.5 ± 11.4, 20 patients with Hodgkin’s disease (HD) and 30 with non-Hodgkin’s lymphoma (NHL). The HD group included 9 patients with β symptoms and the NHL group included 12 with β symptoms. The number of patients with detectable levels of serum IL-1β was significantly higher in each of HD and NHL total groups compared to the controls and in patients with β symptoms compared to the controls. Only in NHL group, serum IL-1β was higher in patients with β symptoms compared to those without. IL-1Ra was found to be significantly higher in patients with lymphoma group compared to controls and there were higher levels in of serum IL-1Ra in patients without β symptoms in both groups (HD, NHL) compared to patients with β symptoms. Significantly higher levels of IL-1sRII were found in patients with HD, with and without β symptoms, compared to controls and in patients without β symptoms compared to patients with β symptoms. In NHL group, we found significant rise in serum IL-1sRII in patients without β symptoms compared to both controls and patients with β symptoms. We conclude that IL-1sRII and IL-1Ra modulate the noxious action of IL-1 and the disturbance of IL-1, IL-sRII and IL-1Ra balance may be responsible for the evolution of symptoms associated with malignant lymphoma.
Introduction

Two forms of interleukin-1 have been cloned, interleukin-1β and interleukin-1α. Cytokines are extracellular signalling glycoproteins that play an important role in many physiological and pathophysiological processes. Interleukin-1 is a highly inflammatory multifunctional cytokine and the margin between clinical benefit and unacceptable toxicity in human is exceedingly narrow\(^{(1)}\). Interleukin-1β is the prominent form of interleukin-1 and the amount of interleukin-1 found in body fluids and in cell supernates is usually tenfold greater than α form. The two forms of interleukin-1 share the same spectrum of multiple biologic properties and recognize the same receptor\(^{(2)}\).

There is an increasing evidence that cytokines are involved in malignancy. IL-1 is believed to be a mediator involved in the production of constitutional symptoms in patients with malignant lymphoma\(^{(3)}\). However, its action is modulated by an early activation of anti-inflammatory cytokines including IL-1 receptor antagonist (IL-1ra)\(^{(4,5,6)}\) which is a naturally occurring modulator of IL-1 that functions by competitively binding to a mediator involved in production of constitutional symptoms in patients with malignant lymphoma\(^{(3)}\). Further modulation takes place at the cytokine receptor level through the regulation of receptor density on target cells and the presence of soluble receptors\(^{(4,6,7)}\). The proinflammatory effects of IL-1 are mediated by IL-1α that remains mainly cell associated.
and by IL-β that is mostly released. These effects are restrained by IL-1Ra, a peptide that binds to IL-1 receptors (IL-1R) but lacks agonist activity. Attempts are being made to use IL-1Ra as a therapeutic agent in diseases modulated by IL-1. IL-1 activity is also modulated by the density of cell bound IL-1R and the presence of sIL-1R, generated by cleavage of the extracellular domain of IL-1R. Two types of IL-1R exist; namely IL-1R type I predominantly expressed on the surface of T cells and fibroblasts with IL-1α, IL-1β and IL-1Ra as ligands, and IL-1R type II (IL-1RII) primarily expressed on the surface of B lymphocytes and monocytes with IL-1β and to lesser extent, IL-1Ra ligands. Transmission of IL-1 signals occurs via IL-1RI whereas IL-1RII functions merely as “decoy” receptor. Cell bound IL-1RI, and sIL-1RI bind IL-1α, IL-1β and IL-1Ra with approximately similar kinetic constants. However, sIL-1RII preferentially binds IL-1β but has lost its affinity to IL-1Ra, a 2000-fold. Thus the presence of IL-1 soluble receptors modulates IL-1 activity.

Malignant lymphoma has been reported as the third most frequent neoplastic disease in Egypt. The prognosis is poorer with the presence of β symptoms. The etiology of these inflammatory signs associated with malignant lymphoma is not fully elucidated and is a matter of more investigations. The therapeutic potentials of interleukin-1 (IL-1) in the cancer therapy has been reported.

The aim of the present work was to assess the serum levels of IL-1, IL-1Ra and IL-1sRII in patients with malignant lymphoma and their role in evolution of β symptoms, and to study the value of IL-Ra in modulating the inflammatory conditions.
Material and Methods

Subjects:

This study was conducted in Microbiology and Immunology Department, Faculty of Medicine, Zagazig University. Fifty patients suffering from lymphoma were selected from Oncology Unit and Internal Medicine Departments, Zagazig University Hospitals in the period between March 1997 to April 1998. Their ages raged from 10 to 68 years, with mean ± SD of 38.5±14.8, 28 males and 22 females. They were diagnosed by thorough history taking and clinical examination, peripheral hemogram, bone marrow aspiration, and histopathological examination. At the time of sampling, none of the patients had received any treatment or had clinical or laboratory evidence of concomitant infectious or inflammatory disease or other malignant disease. According to the histopathological examination of the affected lymph nodes, the patients were classified into two main groups:

1-Hodgkin's disease (HD) group, including 20 patients were of recently diagnosed HD. They were classified according to the presence of β symptoms into two subgroups; HD with β symptoms (9 patients) and HD without B symptoms (11 patients). β symptoms were defined as, unexplained fever with temperature above 38 °C, unexplained weight loss of 10 % or more of body weight in the preceding 6 months and night sweats.

2-Non-Hodgkin's Lymphoma (NHL) group, including 30 patients of recently diagnosed LHL. They were 12 with β symptoms and 18 without.
All patients and control subjects were subjected to the following:

1-Thorough history taking and clinical examination with specific stress on pallor, lymphadenopathy, jaundice, hepatosplenomegaly, fever, loss of weight, and night sweat.

2-Complete blood picture and ESR.

3-Serum concentrations of IL-1β, IL-1Ra and IsRII were measured with ELISA technique using Eurogenetics Kits (Belgium) for IL-1β, Medgenix Kit (Cat. No. 40. 118.02, Biosource Europe S.A., Belgium) for IL-1Ra, and Quantikine TM, R&D system (Minneapolis, USA) for IL-1s RII.

Results

The results are shown in tables (1-6).

Table (1): Serum IL-1β in Hodgkin’s disease

<table>
<thead>
<tr>
<th></th>
<th>Detectable IL-1β</th>
<th>Range</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
<td>%</td>
<td></td>
</tr>
<tr>
<td>All patients (n:20)</td>
<td>11</td>
<td>55</td>
<td>0-182</td>
</tr>
<tr>
<td>Patients with β symptoms (n:11)</td>
<td>7</td>
<td>63.6</td>
<td>0-185</td>
</tr>
<tr>
<td>Patients without β symptoms (n:9)</td>
<td>4</td>
<td>44.4</td>
<td>0-7</td>
</tr>
<tr>
<td>Control (n:10)</td>
<td>1</td>
<td>10</td>
<td>0-0.6</td>
</tr>
</tbody>
</table>

P1 < 0.05 Control versus all patients.
P2 < 0.05 Control versus β symptoms patients.
P3 > 0.05 Control versus non β symptoms patients.
P4 > 0.05 β symptoms versus non β symptoms patients.
Table (2): Serum IL-1β in non-Hodgkin’s lymphoma.

<table>
<thead>
<tr>
<th></th>
<th>Detectable IL-1β</th>
<th>Range</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
<td>%</td>
<td></td>
</tr>
<tr>
<td>All patients (n:30)</td>
<td>14</td>
<td>48</td>
<td>0-125</td>
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<tr>
<td>Patients with β symptoms (n:12)</td>
<td>8</td>
<td>66.7</td>
<td>0-127</td>
</tr>
<tr>
<td>Patients without β symptoms (n:18)</td>
<td>6</td>
<td>33.8</td>
<td>0-0.9</td>
</tr>
<tr>
<td>Control (n:10)</td>
<td>1</td>
<td>10</td>
<td>0-0.6</td>
</tr>
</tbody>
</table>

P1 (< 0.05) : Control versus All patients.
P2 (< 0.05) : Control versus β symptoms patients.
P3 (> 0.05) : Control versus lack β symptoms patients.
P4 (> 0.05) : β symptoms versus lack of symptoms patients.

Table (3): Serum IL-1Ra in Hodgkin’s disease

<table>
<thead>
<tr>
<th></th>
<th>Range</th>
<th>Median</th>
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<tbody>
<tr>
<td>All patients (n:20)</td>
<td>105-3958</td>
<td>1371</td>
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<tr>
<td>Patients with β symptoms (n:9)</td>
<td>108-1645</td>
<td>543.5</td>
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<tr>
<td>Patients without β symptoms (n:11)</td>
<td>378-3895</td>
<td>1527.6</td>
</tr>
<tr>
<td>Control (n:10)</td>
<td>102-286.5</td>
<td>178.0</td>
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</tbody>
</table>

P1 (< 0.001) : Control versus All patients.
P2 (< 0.001) : Control versus β symptoms patients.
P3 (< 0.001) : Control versus lack of β symptoms patients.
P4 (< 0.05) : β symptoms versus lack of symptoms patients.
Table (4): Serum IL-1Ra in non-Hodgkin’s lymphoma.

<table>
<thead>
<tr>
<th></th>
<th>Range</th>
<th>Median</th>
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<tbody>
<tr>
<td>All patients (n:30)</td>
<td>98-3430</td>
<td>398.4</td>
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<tr>
<td>Patients with β symptoms (n:12)</td>
<td>100.5-1252</td>
<td>269.8</td>
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<tr>
<td>Patients without β symptoms (n:18)</td>
<td>109.8-3427</td>
<td>501.8</td>
</tr>
<tr>
<td>Control (n:10)</td>
<td>97-285</td>
<td>178.0</td>
</tr>
</tbody>
</table>

P1 ( < 0.05 ) Control versus All patients.
P2 ( < 0.05 ) Control versus β symptoms patients.
P3 ( < 0.05 ) Control versus lack of β symptoms patients.
P4 ( < 0.05 ) β symptoms versus lack of β symptoms patients.

Table (5): Serum IL-1sRII in Hodgkin’s disease.

<table>
<thead>
<tr>
<th></th>
<th>Range</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients (n:20)</td>
<td>193.5-1562</td>
<td>429.5</td>
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<tr>
<td>Patients with β symptoms (n:9)</td>
<td>193.5-476.6</td>
<td>361.6</td>
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<tr>
<td>Patients without β symptoms (n:11)</td>
<td>241.5-1581</td>
<td>561.5</td>
</tr>
<tr>
<td>Control (n:10)</td>
<td>135.2-396.5</td>
<td>334</td>
</tr>
</tbody>
</table>

P1 ( < 0.05 ) Control versus All patients.
P2 ( < 0.05 ) Control versus β symptoms patients.
P3 ( < 0.001 ) Control versus lack of β symptoms patients.
P4 ( < 0.05 ) β symptoms versus lack of β symptoms patients.
Table(6): Serum IL-1sRII in non-Hodgkin’s lymphoma.

<table>
<thead>
<tr>
<th></th>
<th>Range</th>
<th>Median</th>
</tr>
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<tbody>
<tr>
<td>All patients (n:30)</td>
<td>120.5-1621</td>
<td>356.5</td>
</tr>
<tr>
<td>Patients with β symptoms (n:12)</td>
<td>120.5-758</td>
<td>272.3</td>
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<tr>
<td>Patients without β symptoms (n:18)</td>
<td>228-1630.5</td>
<td>401.5</td>
</tr>
<tr>
<td>Control (n:10)</td>
<td>135-398</td>
<td>334</td>
</tr>
</tbody>
</table>

P1 (> 0.05) Control versus All patients.
P2 (> 0.05) Control versus β symptoms patients
P3 (< 0.05) Control versus lack of β symptoms patients.
P4 (< 0.05) β symptoms versus lack of β symptoms patients.

Discussion

Interleukin –1β (IL-1β) is believed to be an important mediator involved in the production of constitutional symptoms in patients with malignant lymphoma. Its activity is specifically modulated by IL-1 receptor antagonist (IL-1Ra) and IL-1 soluble receptor type II (IL-IsR II). Malignant cells of T-cell origin may secrete cytokines including IL-1 and TNF, that are believed to be mediators in systemic inflammatory response syndrome. The enhancement of tumor metastasis by concurrent inflammatory processes is mainly due to the cytokines TNF and IL-β.

This work entailed assessment of the serum levels of IL-1β, IL-1Ra and IL-1sRII in patients with malignant lymphoma and their role in evolution of β symptoms, and testing the value of IL-1Ra in modulating the inflammatory conditions in infection cases models. Our results showed that the number of patients with detectable levels of serum IL-1β was significantly higher in lymphoma (HD,NHL) compared to
controls and in patients with β symptoms compared to controls (Tables 1,2). Only in patients with NHL, the number of patients with detectable levels of serum IL-1β was significantly higher in patients with β symptoms compared to those without (Table 2). Bodel et al. found that cultured lymph nodes from patients with HD were shown to produce an endogenous pyrogen. Gruss et al. found that IL-1β serum levels were elevated in HD. Ruco et al. found that IL-1 is present in neoplastic cells of both HD and NHL. Xerri et al., using in situ hybridization, found that gene expression for IL-1 and TNFα were observed in Reed-Sternberg cells of 12 out of 19 tumor specimens. Moreover, Denecker et al. showed that the production of IL-1β, TNF-α and IL-1Ra in blood disappears during chemotherapy-induced neutropenia, not only due to the decreased number of producing cells, but also as a result of a decreased production per cell, suggesting a mechanism of downregulation. Diaz and Muro-Cacho, studied macrophage activation in non HL, particularly lymphoepithelioid cell lymphoma, and reported that tumor cells are capable of activating host macrophages followed by IL-1 production with recruitment of additional macrophages accounting for the characteristic histological appearance of this tumor. The activated macrophages are also engaged in a phagocytic antitumoral response. However, our study also revealed that not all patients with lymphoma had detectable levels of serum IL-1β (Tables 1,2). Since a significant amount of Pro IL-1β remains inside the cell and IL-1β also binds to large proteins such as α-macroglobulin, complement, and soluble type II IL-1β receptors, the IL-1β serum levels are low or difficult to be detected unlike TNFα, IL-6, or IL-1Ra. Plasma normally
contains approximately 100 pmol/L of IL-1 sRII, which preferentially binds IL-1β compared with IL-1α and IL-1Ra. The presence of IL-1sRII at 100 pmol/L reduces the detection of IL-1β in clinical samples by 50% (23).

There was no significant difference in the number of patients with detectable levels of serum IL-1β between patients with and without β symptoms in HD (Table 1). Ree et al. (24) found no relationship between IL-1 expression in HD and constitutional symptoms (β symptoms). Shin et al. (3) suggested that the systemic inflammatory reaction caused by IL-1 in lymphoma may be finely adjusted, and balancing or unbalancing between IL-1 and IL-1Ra might be the basis of mechanism through which the constitutional symptoms are elicited. Dinarello (25) stated that studying IL-1 production in disease states as lymphoma can be useful as a marker of disease progression or therapeutic efficacy.

IL-1Ra serum levels were significantly higher in the HD and NHL groups compared to the control group. This elevation was marked in HD. Moreover, the serum IL-1Ra levels in HD and NHL without β symptoms were significantly higher than in those with β symptoms. This finding was consistent with the finding of Gruss et al. (26) who reported that the elevation in IL-1Ra in malignant lymphoma without β symptoms could explain the pathogenesis of these constitutional symptoms through opposing effects of IL-1. Furthermore, the unbalanced production of this cytokine could contribute to the clinical characteristics associated with β symptoms. Secretion of IL-1Ra may be considered a mechanism by which the host is protected from noxious effects of IL-1. Elevated IL-1Ra levels have been reported in many inflammatory conditions such as septic shock, juvenile
rheumatoid arthritis or inflammatory bowel disease (27). IL-1Ra levels can correlate with the severity of the disease (28). In patients with thermal burns, levels of IL-1Ra correlated with the burn area and the highest levels of IL-1Ra were measured in nonsurvivers (29). High levels of circulating IL-1Ra have been observed after surgery, and in asymptomatic persons infected with HIV-1 (25).

There was a significant increase in serum levels of IL-1sRII in the HD with and without β symptoms as compared to the control group ( P<0.05 ). In NHL, patients without β symptoms had significant increase in serum IL-1sRII compared to controls. The HD and NHL groups lacking β symptoms had a significant increase in sIL-1 sRII compared to those with β symptoms. Remarkably, the pattern of plasma IL-1sRII was entirely different from that of IL-1β. Both upregulation of the “decoy” receptor IL-1sRII and shedding of this receptor are of anti-inflammatory mechanisms. Shed IL-1sRII has even stronger anti-inflammatory potencies than cell bound IL-1RII, because shed receptors bind IL-1β with higher affinity (30). During sepsis and after steroid therapy, IL-1sR II mRNA is found to be upregulated (10).

In order to confirm the value of IL-1Ra in modulating the inflammatory conditions, IL-1Ra have been injected in infection cases models before lethal challenge, this resulted in reduction of mortality. On the contrary when injected shortly after challenge, IL-1Ra had little or no effect on reducing death. On the other hand, in acute pancreatitis a dose dependent administration of IL-1Ra late in the disease reduced the severity of tissue damage (31,32). In some models of chronic diseases administration of IL-1Ra after the onset of disease can still dramatically
reduce its severity. Fischer et al. reported that the circulating IL-1Ra during inflammatory stress may serve to reduce the systemic responses to localized IL-1 production when plasma appearance of IL-1β is minimal. So in this situation, the possible therapeutic application of exogenous administration or endogenous stimulation of IL-1Ra may be of benefit. These findings confirm the suggestion that IL-1sRII and IL-1Ra modulate the noxious action of IL-1 and the disturbance of IL-1, IL-1sRII and IL-1Ra balance may be responsible for the evolution of symptoms associated with malignant lymphoma.

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