Aggressive Natural Killer Cell Leukaemia: A Rare and Fatal Disorder

A Gogia*, A Kakar*, SP Byotra*, M Bhargava**

Abstract

Natural killer (NK) cell neoplasms, which include extra-nodal NK/T-cell lymphoma (nasal and extra-nasal) and aggressive NK cell leukaemia, are generally rare, but they are more common in people of oriental, mexican and south american descent. These neoplasms are highly aggressive, and show a strong association with Epstein-Barr virus. Aggressive NK cell leukaemia affects younger patients, who present with poor general condition, fever, and disseminated disease; they often die within a short time from systemic disease or complications such as multi-organ failure.

Aggressive NK cell leukaemia must be distinguished from T-cell large granular lymphocyte leukaemia and indolent NK cell lympho-proliferative disorder, both of which are indolent. We present a case of young Asian male with aggressive NK cell leukaemia who presented with a poor general condition and disseminated disease. The patient had a rapidly progressive disease and died within weeks of diagnosis.

Introduction

Clonal diseases of large granular lymphocyte (LGL) disorders can arise from a CD3+ T-cell lineage or from a CD3– NK-cell lineage. Natural killer (NK) cell neoplasms, which include extra-nodal NK/T-cell lymphoma (nasal and extra-nasal) and aggressive NK cell leukaemia, are generally rare, but they are more common in people of oriental, mexican and south american descent. These neoplasms are highly aggressive, and show a strong association with Epstein-Barr virus. Aggressive NK cell leukaemia affects younger patients, who present with poor general condition, fever, and disseminated disease; they often die within a short time from systemic disease or complications such as multi-organ failure. The peripheral blood and bone marrow show atypical large granular lymphocytes, which exhibit an immunophenotype similar to that of extra-nodal NK/T-cell lymphoma. Aggressive NK cell leukaemia must be distinguished from T-cell large granular lymphocyte leukaemia and indolent NK cell lympho-proliferative disorder, both of which are indolent.

Case History

A 28 year old Asian male was admitted with complaints of fever of 2 months duration along with loss of appetite and weight loss (not quantifiable). The fever was initially low grade and intermittent but progressed to become moderate to high grade and continuous. He also gave history of epistaxis off and on during the last two months. He had past history of chronic ethanolism as he had been taking 10-12 units/day for last 10 years. No other significant past medical or surgical history. There was no significant family history. He was treated by the local physician without any relief. He was admitted in an outside institute without any relief. He was admitted in an outside institute where he was evaluated. He was found to have fever with hepato-splenomegaly, anaemia and thrombocytopenia. His CT scan abdomen showed hepato-splenomegaly with small lymph nodes in the porta-hepatitis and para-aortic region. As the patient had significant anaemia and thrombocytopenia, he received multiple blood and platelet transfusions. His bone marrow aspiration and biopsy done there showed erythroid hyperplasia. On clinical grounds, he received empirical anti-tubercular treatment but developed hepatitis so anti-tubercular treatment was modified and non-hepatotoxic drugs started. Patient did not show any improvement and was shifted to our institute. On arrival at our institute patient was febrile with Temperature of 39°C, Pulse 100/min, BP 130/80 mmHg. He had pallor and icterus with pedal oedema. There was no generalized lymphadenopathy, raised JVP or cyanosis. On investigation, he was found to have anaemia with thrombocytopenia (Hb 7.6 gm/dl, platelets 25000/cumm) along with significantly raised bilirubin (total bilirubin 20.6 gm/dl with direct fraction of 12.6 gm/dl), the AST 463 IU/L, ALT 355 IU/L, Alkaline phosphatase of 223 IU/L, BUN/Creatinine 27.9 mg/dl/2.5 mg/dl. During hospital stay, he developed pancytopenia and the haematological parameters are shown below:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>21/04/2007</th>
<th>24/04/2007</th>
</tr>
</thead>
<tbody>
<tr>
<td>TLC (1/microl)</td>
<td>3,800</td>
<td>1,800</td>
</tr>
<tr>
<td>Hb (g/dl)</td>
<td>7.1</td>
<td>6.7</td>
</tr>
<tr>
<td>RBC count (1/microl)</td>
<td>2.46x10⁶</td>
<td>2.31x10⁶</td>
</tr>
<tr>
<td>Hct (%)</td>
<td>19.6%</td>
<td>18.4%</td>
</tr>
<tr>
<td>MCV (fl)</td>
<td>79.7 fl</td>
<td>79.9 fl</td>
</tr>
<tr>
<td>MCH pg</td>
<td>28.7 pg</td>
<td>28.9 pg</td>
</tr>
<tr>
<td>RDW (%)</td>
<td>17.9%</td>
<td>17.2%</td>
</tr>
<tr>
<td>PLT (1/microl)</td>
<td>22,000</td>
<td>15,000</td>
</tr>
</tbody>
</table>

A bone marrow aspiration and biopsy (Figs. 1 & 2) were done and a possibility of a large granular cell lymphocytic leukaemia and flow cytometry pictures showed ill-defined cluster of abnormal cells displaying intermediate FSC/SSC and bright CD 45 expression. These cells express moderately bright CD56 with co-expression of CD 38 in 335 cells, cytoplasmic CD3 with aberrant expression of CD 7. These cells lack c MPO, Ccd79a, surface CD3, CD16, CD5, CD4 and CD8. These findings were found consistent with NK cell leukaemia. (Fig. 3). So in view of the laboratory findings and the clinical picture a diagnosis of aggressive NK cell leukaemia was made. As NK cell leukaemia has association with EBV, Anti-IgG EBV was positive. An ALL
like treatment regimen was decided for treatment but as patient had severe liver dysfunction, the treatment could not be started and over next 2 weeks patient expired.

Discussion

Malignancies of NK cell are rare, aggressive disorders that cause both leukaemia and extra-nodal infiltrations, with a predilection for nasal cavity. Patient with NK cell leukaemia tend to be younger than the patients with extra-nodal disease and present with B symptoms, bone marrow involvement, organomegaly, high white blood cell counts and, in some patients, hemophagocytic syndrome. Response to chemotherapy is usually poor and most patients succumb within days to months to their disease.

LGL leukaemia comprises of 2-5% of all T-cell /NL cell malignancies with only 400 cases reported in medical literature. The aggressive type of NK cell leukaemia occurs at a younger age with a median age of 39 years and with a higher prevalence in Asia and South America. Fewer than 100 cases have been reported in the literature. The aggressive NK cell is usually a rapidly progressive disorder associated with Epstein Barr virus (EBV). The disease is usually not responsive to conventional chemotherapy and the median survival is 2 months.

Clinico-pathological Characteristics of Large Granulocytic Leukaemia (LGL)

NK cell marker CD56 is typically detected in NK cell LGL leukaemia. The immunophenotype of this subtype is similar to that of the nasal type of NK-cell/T-cell lymphoma that is CD2+CD56+CD3ε+. The most common immunophenotype is CD2 (+), surface CD3 (-), cytoplasmic CD3 (+), CD56 (+). In the differential diagnosis, this aggressive NK-cell malignancy must be distinguished from indolent chronic NK-cell leukaemia and benign chronic NK-cell lymphocytosis, which are not associated with EBV. Induction chemotherapy with an intensive acute lymphoblastic leukemia (ALL)–like regimen followed by allogeneic stem cell transplantation has been used with curative intent in a limited number of cases but as only few cases are reported no clear guidelines regarding management are available.
Conclusion

Aggressive NK cell leukaemia is a rare condition. These neoplasms are highly aggressive, and show a strong association with Epstein-Barr virus. Aggressive NK cell leukaemia affects younger patients, who present with poor general condition, fever, and disseminated disease; they often die within a short time from systemic disease or complications such as multi-organ failure.

References