History of significant researches of leukemia and its subtypes

Education, Learning

Leukemia as a type of malignant hematologic neoplasm has probably always existed as far as the science of medicine is concerned. Yet it was our understanding of leukemia which changed tremendously during the course of the last 200 years. According to many authors, French surgeon and anatomist Alfred Velpeau was the person to be credited with the first reported case of leukemia in the modern history of medical research. However, it was the German physician and pathologist Rudolf Virchow who coined the term “ leukemia” some 20 years after the first published case by Velpeau. According to T. Hamblin from the Department of Hematology of the Royal Bournemouth Hospital in UK, Virchow published another nine cases, most of them having splenic involvement. Due to one of the Virchow’s patients having general lymphadenopathy in absence of splenic involvement, he classified leukemia as being either “ splenic” or “ lymphatic”. The latter is argued by Hamblin to be the first recognized case of CLL.

Virchow, being a skilled pathologist went on further to distinguish between the agranular leucocytes present in lymphatic leukemia and granular leucocytes of the splenic type of disease. Further breakthrough in understanding of leukemia came during the second half of 19th century through works of Ernst Neumann, who was the first man to propose the idea of bone marrow as the place of origin for blood cells. According to Hamblin, he also succeeded to differentiate between two distinct types of leukemia according to involvement of bone marrow. The first one was characterized by granular cells and pyoid appearance. Neumann classified the second type as lymphadenoid and having cells which lacked cytoplasm and had

homogenous nuclei [4]. Moreover, the works of Paul Ehrlich and his, at the time revolutionary stains, made the clear distinction between cell compartments and different microscopic features possible. This brought upon a possibility of distinguishing between different types of leukemia. The significance of Ehrlich’s works was recognized worldwide as he received the Nobel Prize for Medicine in 1908.

The beginning of the 20th century brought with itself new possibilities for classification of leukemia due to Ehrlich’s staining methods. His Viennese based colleague Wilhelm Türk published what are today known as one of the first diagnostic criteria for different types of leukemias, including CLL and its similarities/differences with other types of leukemia. Paul Ehrlich also addressed the concept of autoimmunity and its relation to hemolysis and argued that it would be counterproductive for human body to make autoantibodies directed against its own structures. The existence of such antibodies was proven some three years after his publication. Some half a century later, first clues on hemolytic nature of anemia in CLL were brought by Berlin.

Further research done by Wasserman showed that hemolytic anemia in CLL often tested positive for Coombs test and that it was autoantibody mediated which gave it the name hemopathic hemolytic anemia. What was described in his works went on to be the forerunner of autoimmune hemolytic anemia (AIHA), which was later shown to be present in one tenth to one quarter of all CLL patients. In terms of thrombocytopenia, first findings regarding its existence in CLL patients descend from the third decade of 20th century.

Minot and Buckman recorded it in approximately 50% of the patients they diagnosed with CLL. It took some forty years until the autoimmune genesis of immune thrombocytopenia (ITP) in CLL was discovered.

As the century progressed, technical and scientific advances made it possible for researchers to acquire more insight into the nature of lymphocytes. Concepts such as cell-mediated and antibody mediated immunity were postulated for the first time and specific research on this topic was conducted. The understanding of lymphocytes also changed dramatically thanks to animal studies and studies on burn victims involving skin grafts [16-20]. According to Hamblin, the second renaissance in research of CLL came in the seventies with studies on immunodeficient children and possibility of differentiating between T- and B-Cells which in turn made determination of the immunophenotype of CLL lymphocytes possible.

As the understanding of leukemia and its subtypes including CLL involved, more and more steps were undertaken to develop a staging system which would predict patient’s survival. The first staging system to be introduced was Kanti Rai’s one, based on patients clinical findings and published in 1975. The aim of Rai and his colleagues was to identify easily measureable parameters which would help clinicians to assess patient’s survival, as at this point in time no such system existed. Their work was based on the previous findings by Dameshek which involved the absolute white blood across different disease stages. Furthermore, they also included the findings of Boggs and Zippin which assessed the abnormalities present at the time of

diagnosis with respect to survival times. Therefore, Rai et al. developed a staging system which was based on the degree of lymphocytosis measured through peripheral white blood count or bone marrow biopsy, lymphadenopathy, liver and spleen enlargement, as well as anemia and thrombocytopenia.

Two years later his French colleague Jacques-Louis-Binet published a similar staging system which was in essence a modification of his American colleagues' system. However, Binet's staging system included a smaller cut-off value for the absolute white blood count, which resulted with longer overall median survival. However, there was no significant difference in survival time when the groups were compared to the equivalent groups in Rai's staging system. As it was often the case with medical research throughout the history, the two staging systems reflected a different approach to the same problem, with Rai's staging system representing the American and Binet's the European side of the same coin. The two staging models created by Rai and Binet, still represent an important basis for decision-making in clinical setting.

Despite their relatively easy-to-use nature and the fact that they relied on relatively inexpensive examinations for determining the survival, the two methods nevertheless had their weaknesses. Even Binet himself recognized the redundancy of so many stages within his system. This resulted in the reassessment of his previous work and the number of stages was reduced from five to three which simplified clinical assessment of patients [30]. As the time progressed, new efforts were undertaken do develop new

prognostic models and identify specific biochemical and histologic factors which had an impact on overall survival. Rozman and Montserrat were able to identify a diffuse pattern of bone marrow infiltration as being predictive of higher risk and shorter survival times. They also undertook the first steps in defining the parameters which could determine the kinetics of the disease and identified a longer lymphocyte doubling time as having a good prognostic value in terms of overall survival and time to first treatment.

The last decade of the 20th century brought with it an enormously important finding in terms of molecular cytogenetic changes associated with CLL. The discovery of the Philadelphia chromosome in chronic myelocytic leukemia sparked an interest in chromosomal changes associated with the other types of leukemic diseases. Up to this point, trisomy 12 represented one of the few known chromosomal abnormalities found in CLL. In their multicenter study involving patients from five different centers across Europe, Juliuss et al. evaluated patients with diverse chromosomal aberrations. They succeeded in showing that patients with chromosomal abnormalities had poorer overall prognosis compared to those with normal karyotype. Overall, aberrations in ten different chromosomes were identified, most of them being translocations and deletions in different genes. Hence, the first bigger step into defining the prognostic significance of different genetic findings was taken.

Another important area in CLL research was the study of B-cell receptors, which progressed from the studies on clusters of differentiation in leucocytes from the eighties. Foroni et al. showed that most of the leukemic cells in CLL

exhibited rearrangement in one of the two genes coding for the variable sequence of the immunoglobulin heavy chain (IgHV). Further body of research showed that B-CLL cells were able to undergo a somatic mutation in the aforementioned gene which rendered some of them resistant to the antibody therapy directed towards specific sequences of their surface immunoglobulins. Later studies showed that B-CLL cells with non-mutated IgHV segments tend to exhibit a higher degree of autoimmunity mediated through production of polyreactive antibodies and higher affinity for them. Such phenomenon was argued to stimulate the leukemic cells and bring about the survival of clonal B-cell populations at high risk for CLL-transformation.

However, it wasn’t until the end of 20th century and works of Matusda and Cook, that the gene locus of VH gene was sequenced in its entirety. Up to this point it wasn’t entirely clear whether the majority of the CLL patients had either mutated or unmutated VH genes. Later research showed that CLL was comprised of two different cell types with different clinical image and course of disease. Hence, a CLL arising from immature B-cells and having unmutated VH gene tends to have a rather rapid progression and shorter survival times.

Another issue that rendered determination of CLL’s origin difficult was the fact that most of but not all of the CLL-lymphocytes exhibit CD5 molecules on their surface. This was also shown to be true with regard to other molecular markers such as CD38, which correlated with the degree of mutated VH gene and was shown to be a risk factor in CLL. These findings

shifted the understanding of CLL as a disease of accumulated immature cells towards a more diverse disease with leukemic cells arising from different stages of B-cell development.