Review

The ever evolving Hematopathology

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Abstract: Following the first case series of Hodgkin lymphomas described by Thomas Hodgkin in 1832, the field of hematopathology has traversed the (gross and microscopic) morphological, immunological, and genetic eras, to arrive finally at the molecular era. With the efforts of generations of outstanding hematopathologists, each subsequent era has advanced the field further. Meanwhile, as the field has evolved, the role of pathologists has also grown and changed from a histopathology curator to a clinical diagnostician and finally to a vital member of the patient care team. This article, which marks the inaugural issue of *Hematopathology*, will briefly review milestones in the history and development of hematopathology since Thomas Hodgkin first pioneered the field.

Keywords: Hematopathology, Classification, History

Introduction

Although Pathology is as ancient as 17th century BC Egyptian medicine [1], Hematopathology can only be traced back to 1832 when Thomas Hodgkin [Figure 1, left panel], then a physician at the Guy's Hospital in London, England, first described seven autopsies with "absorbant glands and spleen with cartilaginous nodules". In his 47 page case series, he described these glands as "tumors" [2], which were later called "Hodgkin's disease" by his successor Samuel Wilks [3]. Thirteen years later in 1845, Rudolf Virchow [Figure 1, right panel] in Prussia observed an abnormally large number of white blood cells in a patient with "Weiss blut" (white blood) [4], later named "leukämie" [5], and he suggested that it was a neoplastic process. In 1844, Samuel Solly described the first documented case of multiple myeloma [6]. Two years later, an English grocer Thomas McBean presented to William Macintyre with "broken bone" pain and heat soluble "animal matter" in urine [7]. In 1873, "multiple myeloma" was coined to this distinct disease by J. von Rustizky to indicate its clinical presentation and bone marrow involvement [8]. Nowadays, Hematopathology became a discipline that studies the diseases of lymphoid tissues, spleen, blood, and bone marrow. But historically, it has experienced four eras of progress: the morphological era, the immunological era, the genetic era, and the molecular era.

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Morphological Era

The morphological era might have begun as early as in 1666 when Marcello Malpighi reported a similar disease as Thomas Hodgkin later described [2]. The application of microscope in pathology indeed saw the golden age of this era. Just over a decade after Thomas Hodgkin's case series, John Bennett in Scotland and Rudolf Virchow in Prussia began

to examine leukemia cells with microscopes [4, 9]. When Virchow was hired as the Chair of Pathological Anatomy at the University of Würzburg In 1849, he developed his famous *Cell Theory* and urged his medical students to "think microscopically" [10]. The detail of blood cells could not be examined until 1891, when a Russian physician Dmitry Romanowsky developed a technique for staining blood cells using a mixture of Eosin and modified Methylene blue [11]. This technique was modified later by James Wright in 1902 [12], and Gustav Giemsa in 1904 [13]. Now the Wright-Giemsa stain is routinely used for the evaluation of blood and bone marrow cells. The idea of using a mixture of acidic and basic dyes gave rise to the Hematoxylin-Eosin stain, the most widely used stain in histopathology. The advancement of microscopy and staining techniques enabled Carl Sternberg and Dorothy Reed to independently describe the morphology of Hodgkin disease and to understand the disease in more depth [14, 15]. Because of this, the characteristic cells they described in Hodgkin disease were named Reed-Sternberg cells. Based on the morphology of Reed-Sternberg cells and the associated spectrum of reactive background, Robert Lukes and James Butler proposed the Rye Classification of Hodgkin Disease in 1966 (Table 1) [16]. In 1956 and later modified in 1966, Rappaport Classification of Malignant Lymphomas was carved out by Henry Rappaport (Table 2) [17, 18], which was fine-tuned in 1974 by the Lukes and Collins Classification of Malignant Lymphomas [19]. During this time, a group of seven hematopathologists from Britain, France, and U.S. proposed a unified French-America-British (FAB) Classification of the Acute Leukemias (Table 3) and Myelodysplastic Syndrome based on morphological and cytochemical findings [20]. The FAB Classification experienced two subsequent modifications in 1982 [21] and in 1985 [22], and some of the distinct diseases defined by this morphological classification were later confirmed by cytogenetic studies [22, 23]. This classification has guided numerous clinical trials for many years [24] and its significance is still under discussion [25].

Figure 1: Pioneers of Hematopathology
Left panel: Thomas Hodgkin. English physician, 1798-1862; Right panel: Rudolf Carl Virchow, Prussia physician, 1821-1902.
(Thomas Hodgkin. Reproduced courtesy of Gordon Museum, Guy's Hospital, GKT, King's College London. Rudolf Virchow. Reproduced courtesy of History of Medicine Division, National Library of Medicine, Bethesda, MD.)

Limited by the lack of immunophenotyping and genetic information, each classification had its *pros* and *cons*. However, these classifications were nonetheless important milestones in the history of Hematopathology and the wisdom associated with these classifications still guide us in nowadays routine lymphoma workups. To resolve the conflicts between the different lymphoma classifications, National Cancer Institute organized a conference in 1982 and brought forward the Working Formulation on lymphomas [26]. Working Formulation for the first time recognized that non-Hodgkin lymphoma

Table 1: Rye Classification for Hodgkin Disease

Histologic types
Lymphocyte predominant (Lymphocytes & histiocytes)
Nodular
Diffuse
Nodular sclerosing
Mixed cellularity
Lymphocyte depletion (Reticular)

Note: Modified from [16].

is distinct from Hodgkin disease. It separated the non-Hodgkin lymphomas into four major classes: 1) low grade; 2) intermediate grade; 3) high grade; and 4) miscellaneous. Solely based on morphology, the Working Formulation quite accurately interpreted the biology of lymphomas and was used to stratify patients in lymphoma clinical trials for decades.

Immunological Era

Although immunohistochemistry was spearheaded by Albert Coons at Harvard Medical School, who in 1942 localized antigen in tissues by conjugating a fluorescent chemical group to an antibody specific to the antigen [27], immunophenotyping was not as widely used until 1974 when flow cytometry instruments were developed [28]. Using specific antibodies, Elaine Jaffe et al. in 1974 identified that the so called "nodular lymphomas" originated from the follicular center B cells [29]. The same year, Karl Lennert in Germany developed the Kiel Classification of Malignant Lymphomas that for the first time separated non-Hodgkin lymphomas into T-cell and B-cell types [30]. Hybridoma technology by César Milstein and Georges Köhler in 1975 [31] indeed made specific antibodies readily available to the clinical labs, which markedly decreased the costs and facilitated the use of immunophenotyping in diagnosing diseases. In 1982, a T-cell marker CD5 (Leu-1) was found to be aberrantly expressed in chronic lymphocytic leukemia and mantle cell lymphoma [32]. The next year, Harold Stein et al. in Germany found that Hodgkin lymphoma cells could be identified using an antibody against Ki-1 (CD30) [33]. Peter Isaacson et al. defined the B-cell lymphoma of mucosa-associated lymphoid tissues (MALT) as a distinct entity [34]. Curt Civin et al. at Johns Hopkins Hospital identified a new antigen My-10 (CD34) in the KG-1a leukemia cell line [35]. HPCA-1, the monoclonal antibody against My-10, was used in subsequent years by many physicians for leukemia classification and stem cell therapy. In 1984, Nancy Harris et al. at Massachusetts General Hospital found that CD10 was a characteristic marker for follicular lymphomas [36]. Two years later, Ronald Dorfman et al. at Stanford University identified CD15 in Hodgkin lymphoma cells and separated the nodular lymphocyte predominant Hodgkin lymphoma from classical Hodgkin lymphoma by staining for CD45 [37]. Discovery of aberrant expression of cyclin D1 in mantle cell lymphoma in 1994 separated this entity from chronic lymphocytic leukemia both immunophenotypically and biologically [38]. In contrast to the B-cell lymphomas classified depending on the cytology and nodal architecture, T-cell lymphomas were largely categorized based on the involved organs. As a result of years' immunologic studies, a Revised European American Lymphoma (REAL) Classification came into being [39], which became the prototype of the later WHO Classification of Haematopoietic and Lymphoid Tumors. Pathologists also created the concept of "grey zone lymphomas" by recognizing the overlapping immunological features of several common lymphoid malignancies [40–42]. These overlapping morphologic and immunophenotypic features might reflect a dynamic transition between various lymphomas [43].

Table 2: Rappaport Classification of non-Hodgkin Lymphomas

Well-differentiated lymphocytic lymphoma = small lymphocytic lymphoma
Poorly differentiated lymphocytic lymphoma = follicular center cell lymphoma with a large component of small-cleaved cells
Histiocytic lymphoma = large cell lymphoma

Note: Modified from [17, 18].

Genetic Era

The causes of leukemia and lymphoma had long puzzled hematopathologists. In 1950s, most hematopathologists believed that viruses were the leukemogenic and lymphomagenic agents, particularly when Denis Burkitt described an aggressive malignant lymphoma in the Epstein-Barr virus epidemic tropical Africa [44] and Friend virus was found to cause mouse leukemia [45]. This belief was shattered in 1960 by Peter Nowell at the University of Pennsylvania and David Hungerford at Fox Chase Cancer Center, who jointly showed that cancers arose because one cell with a chromosomal anomaly divided into many, as opposed to numerous cells simultaneously becoming cancerous [46]. That small

Table 3: French-American-British Classification of Acute Myeloid Leukemias

Leukemia type	Cytological feature	Criteria
Myeloblastic leukemia without maturation (M1)	Some evidence of granulocytic differentiation; Type I & II blasts with non-granular cytoplasm and one or more distinct nucleoli	Blasts ≥90% of nonerythroid cells; ≤10% maturing granulocytes; ≥3% positive for MPO, or SBB
Myeloblastic leukemia with maturation (M2)	Maturation at or beyond the promyelocyte stage; Type I & II blasts present; early maturing cells with fine nuclear chromatin, one or two nucleoli, and abundant cytoplasm with variable granules that sometimes coalesce	Blasts >30% & ≤89% of noneryhroid cells; <20% monocytic cells; >10% maturing granulocytes
Promyelocytic leukemia (M3)	Majority of the cells are abnormal promyelocytes: (a) cytoplasm with heavy azurophilic granulation; (b) nucleus varies in sizes and shapes, often reniform or bilobed; (c) bundles of Auer rods in cytoplasm; (d) micrugranular variant with bilobed nucleus	? >30% $^{\Phi}$
Myelomonocytic leukemia (M4)	Both granulocytic and monocytic differentiation in varying proportions. Resembling M2 except the promonocytes and monocytes exceeds 20% of the nucleated cells M4eo variant: Eosinophils with large basophilic granules and single unsegmanted nucleus; positive for CAE and PAS	Bone marrow: blasts >30% of nonerythroid cells; granulocytic lineage including myeloblasts ≥30% & <80% of nonerythroid cells; monocytic lineage (by NSE) >20% of nonerythroid cells Peripheral blood: monocytes ≥5 x 10^9/L if lysozyme concentration > 3 times of the normal value and increased marrow monocytic components
Monocytic leukemia (M5)	(a) Poorly differentiated: large blasts with delicate lacy chromatin, one to three prominent nucleoli, and abundant cytoplasm showing pseudopods and rare azurophilic granules (b) Differentiated: monoblasts, promonocytes, monocytes	Sum of monoblasts, promonocytes, and monocytes ≥80% of nonerythroid cells (a) Monoblasts ≥80% of all the monocytic cells; (b) Monoblasts <80% of all the monocytic cells
Erythroleukemia (M6)	Type I & II blasts present increased erythroblasts showing dyserythropoiesis (>10%)	Blasts ≥30% of nonerythroid cells; erythroblasts >50% of all nucleated cells

Note: Modified from [20–22]. Φ: According to reference [21], "over 30% bone marrow blasts will suffice for the diagnosis of AML in any of its forms (M1-M6)." Acute promyelocytic leukemia (AML-M3) often has <30% blasts.

abnormal chromosome was called Philadelphia chromosome (Ph), named after the city of its discovery. In 1972, Janet Rowley at University of Chicago found that this small chromosome was the result of two chromosomal breaks and swapped end translocation between chromosomes 9 and 22 [47] right after her identification of the reciprocal translocation between chromosomes 8 and 21 in acute myeloid leukemia cells [48]. In 1977, her lab further identified the t(15;17) in acute promyelocytic leukemia cells [49]. In addition, various other relatively nonspecific chromosomal abnormalities, such as -Y, -7, 5q-, +8, 20q-, were identified in other myeloid leukemias [50]. In her Editorial on *Blood*, Janet Rowley concluded, "Chromosomal analysis of bone marrow cells by use of banding techniques has become an integral part of the careful investigation of virtually any group of patients with a particular hematologic disorder and may prove useful in guiding the clinician in the prognosis and therapy of these disorders [50]. Subsequently, hematologic genetics boomed for a decade. The t(8;14) was identified in Burkitt lymphoma in 1976 [51], t(11;14) in mantle cell lymphoma in 1979 [52], trisomy 12 in chronic lymphocytic leukemia in 1980 [53], t(14;18)(q23;q21) in follicular lymphoma [54] and 11q23 abnormalities in acute monocytic leukemia in 1982 [55], and inv(16) in acute myelomonocytic leukemia in 1983 [56]. Up to date, hundreds of cytogenetic abnormalities have been identified in hematopoietic and lymphoid neoplasms [57].

Molecular Era

The year 2000 not only greeted a new millennium, but also opened a new chapter for Hematopathology. The 1st edition of WHO Classification of Haematopoietic and Lymphoid Tumors concluded all the major advances in over a century's constantly evolving Hematopathology [58]. We also marched into a productive molecular era marked by two remarkable works on molecular classification of leukemias and lymphomas [59, 60]. The revolutionary PCR assay [61] and automated sequencing [62] enabled our hematopathologists to apply the cutting edge technologies in clinical labs. Still in mid 1990s, a group of German pathologists using "single cell PCR" technique showed clonal immunoglobulin gene rearrangement in Hodgkin-Reed-Sternberg cells [63], confirming that "Hodgkin disease" is a *bona fide* B-cell lymphoma. The solution of whole human genome [64, 65], and invention of cDNA microarray [66] and proteomics [67] facilitated the molecular classification of hematological and lymphoid diseases. In 1999, Golub et al. using gene expression monitoring DNA microarray classified acute lymphoblastic leukemia and acute myeloid leukemia [59]. Almost the same time, diffuse large B-cell lymphomas were also classified into germinal center B-cell (GCB) like and activated B-cell (ABC) like types [60]. Gene expression array approach confirmed the molecular "grey zone" between classical Hodgkin lymphoma and primary mediastinal large B-cell lymphoma [68]. In 2006, American and European hematopathologists independently identified the MYC-positive diffuse large B-cell lymphomas and MYC-negative Burkitt lymphomas [69, 70]. Zhan et al. also classified multiple myeloma using molecular approaches [71]. Global genomic sequencing of the leukemia and lymphoma cells led to the discovery of numerous point mutations that not only drive the neoplastic process, but also provide the molecular targets for specific therapies [72]. The most successful example is the imatinib that was designed based on the discovery of BCR-ABL activated tyrosine kinase in the chronic myelogenous leukemia cells [73]. Nowadays, targeted therapy is no longer a luxury thanks to our molecular diagnostics labs performing the mutational analyses for all types of hematological and lymphoid malignancies. The role of hematopathologists also evolved from a pure diagnostician to a role more and more actively involved in patient management.

Conclusion

As compared to Pathology, Hematopathology is a relatively young subspecialty. Hematopathologists did not have their identity until 1974, when the first organization dedicated to Hematopathology, European Lymphoma Club, was formed and Karl Lennert organized its first meeting in Kiel, Germany [74]. Later in 1981, Society for Hematopathology (SH) was founded in the United States by Costan Berard and Ronald Dorfman [75]. In 1988, European Association of Hematopathology (EAHP) was founded by Karl Lennert in Geneva, Switzerland [74]. Since then, the two largest Hematopathology organizations (SH and EAHP) in the world have collaboratively organized numerous workshops. In November of 2013, a group of enthusiastic San Diego hematopathologists also founded their own Hematopathology Society.

With the constantly advancing science and technology, Hematopathology keeps evolving to a higher and higher level. As Nancy Harris mentioned at the Kevin Salhany Memorial Lecture of the University of Pennsylvania, "None of us can avoid three things in our life time – tax, death and a new WHO Classification (of hematopoietic and lymphoid tumors)."

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