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Transformation of follicular lymphoma – Why does it happen and can it be prevented?

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ABSTRACT

Follicular lymphoma is a clinical disease with a multitude of presentations and behaviors. Although infrequent, transformation of follicular lymphoma to a more aggressive behaving subtype – prototypically diffuse large B-cell lymphoma – confers a substantially adverse prognosis. There is no consensus for optimal management after transformation is recognized. Historically considered a distinct clinical event, this review highlights the multiple subclinical transformational events that either variably or cumulatively result in clinical recognition of transformed follicular lymphoma. Known and suspected events include genetic and epigenetic perturbations, metabolomic changes, and alterations in the microenvironment. This diverse spectrum of pathways leads to heterogeneous clinical presentations and outcomes of transformed follicular lymphoma. Current options for prevention of transformation are limited to known strategies of managing follicular lymphoma before the transformation is recognized. Although most retrospectively analyzed studies suggest an association of lower transformation rates with early systemic therapy, specific components of therapy such as anti-CD20 antibodies, anthracyclines, or purine analogues are less strongly associated with "preventative' value. Thus, the goal of preventing transformation is of limited value among all factors that go into decisions on early management of follicular lymphoma. Future opportunities to prevent clinical evidence of transformation will benefit from early detection of markers of subclinical transformation and development of therapies to specifically target the biology implied by those markers.

1. Transformation of follicular lymphoma

1.1. Why is it of interest and what is the scope of the problem?

Follicular lymphoma (FL) is a disease commonly characterized as incurable, though relatively slow in pace of growth with a median life expectancy of 15–20 years [1], and systemically treatable with expectations of somewhat extended response at the cost of limited toxicity [2]. As patients assimilate and adjust to the horror of incurable cancer, the lymphoma care team often prioritizes education to provide some comfort – especially since systemic therapy may not be indicated early after diagnosis. Somewhere in the educational effort, following "indolent", "low grade" "responsive to therapy" "long remissions" "gentle treatments" and "many years", the conversation gets around to "transformation" much like a depiction of rainbow-

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colored fish, crabs, coral and sea turtles as occupants of the reef gets around to sharks. Along with early treatment failure following immunochemotherapy [3–6], transformation to high grade lymphoma – prototypically diffuse large B-cell lymphoma – represents the greatest fear for patients, their loved ones, and medical teams as the anticipated long journey with FL is commenced.

Several recent reports of large cohorts of varying origin and methodology have provided a fairly consistent depiction of the frequency and implications of follicular lymphoma transformation (tFL) [6–17]. In the setting of immunotherapy and chemotherapy treatment options, the risk of transformation to DLBCL is 2–3% per year for FL patients for at least the first 10 years after which the data become less reliable though some series hint at lower rates farther out from diagnosis [14]. Outcomes following transformation are unfortunate and inferior to those of patient with FL who do not experience transformation but are no longer recognized as universally catastrophic as they had been in the twentieth century with median survival after transformation in most series between 4 and 5 years [7,9,13,15,16]. Survival is reported to be better for patients with lower FLIPI [18] scores, those previously anthracycline naïve, and for patients who transform later following FL diagnosis as opposed to transformation within the first 18 months [7,12,13]. Management strategies following recognition of transformation are numerous and without much consensus or consistent success [9,12,13,15,16].

Given the generally poor outcomes and unsatisfactory understanding of optimal management after transformation is clinically recognized, seeking better understanding of cause and potential prevention of clinically apparent transformation of follicular lymphoma is warranted. Two central tenets of this review will be heightened appreciation of the diversity of tFL and of the complex dynamics of preclinical transformation events.

2. Why does transformation happen?

2.1. Transformed follicular lymphoma is a heterogeneous disease with heterogeneous origins (Table 1)

A simple definition for transformed follicular lymphoma is without universal consensus. The gold standard for diagnosing transformation in FL is generally recognized as biopsies demonstrating: a) FL grade 1, 2, or 3a and b) at a distant place or time histological demonstration of an increase in the proportion of large centroblasts infiltrating lymph nodes leading to effacement of the follicular architecture [19]. Strictly speaking these histologies should be confirmed to be clonally related. This gold standard is often adapted loosely in clinical series and in clinical practice. Such biopsies may be sequential, and some investigators historically restricted the definition of tFL to those scenarios where such biopsies were separated by at least 6 months [10,20,21]. Some newer published series of tFL, however, evaluated patients with concurrent identification of follicular lymphoma and diffuse large B-cell Lymphoma (DLBCL) either in a single biopsy [16] (alternatively referred to by others as composite lymphoma) [22,23] or in multiple synchronous biopsies (alternatively referred to as discordant lymphoma) [23,24]. Furthermore, some investigators accept a clinical definition of transformation in patients for whom no biopsy demonstrating DLBCL is available. Clinical criteria proposed by Al-Tourah et al. including a sudden rise in LDH, rapid discordant localized nodal growth, new B symptoms, hypercalcemia, or new extranodal sites of disease are the most often cited for inclusion in tFL series [8]. FDG-PET scans are also advocated by some as adjuvant determinants of transformation, with standardized uptake values between 10 and 17 proposed as a surrogate for pathological evidence of transformation [25–27]. Given recent advances in the appreciation of multiple pathways by which transformation can emerge from subclinical genetic alterations to the full blown clinical manifestations, this review will adapt an inclusive attitude when considering tFL and will endeavor to point out examples with a marginal or conditional definition for tFl when relevant.

Histologic diversity of follicular lymphoma upon transformation is evident with the most common histology being DLBCL [8,19] followed by the entity previously categorized as Burkitt-like lymphoma, subsequently as B-cell lymphoma unclassifiable with features intermediate between DLBCL and Burkitt lymphoma, and most recently as high grade B cell lymphoma NOS [28–30]. Uncommonly, histologic and immunophenotypic characteristics of tFL overlap with acute lymphoblastic leukemia/lymphoma or other blastoid histologies [31,32]. Even the DLBCL histologies can be diverse with 80% marking as germinal b-cell like origin, yet 16% marking as activated b-cell like origin [33], and MYC rearrangement or overexpression is seen in nearly half of biopsies [34].

Clinical diversity of FL upon transformation is evident by timing of the recognition of transformation. Some authors recognize transformation at the time of lymphoma diagnosis when both DLBCL and FL histologies are found at initial evaluation. In the largest reported series of these “de novo transformed” patients, the National LymphoCare Study (NLCS) demonstrated probability of survival with de novo transformation was favorable when compared to patients with a more traditionally defined sequential transformation and not clearly different than FL patients in whom no transforming event was identified [16]. In another series, patients with recognized transformation within 18 months of FL diagnosis had a distinctly adverse 5 year survival rate relative to those with later transformation (66% vs 22%) [13]. Additionally, some patients are immunochemotherapy naïve at clinical transformation, some are simply chemotherapy naïve, and others have variable prior exposure to anthracyclines, alkylating agents or purine analogues [7,8,11,13,14,16,17].

Genetic diversity of tFL is profound with studies suggesting the transforming biology cannot be accounted for by disruptions of a unifying pathway. Early studies implicated acquisition of mutations in p53 [35,36] or p16 [37] in paired biopsy samples and at least altered gene expression if not frank mutation in MYC in many cases [38,39]. More recently, eloquent dissection of abnormalities in MLL2, EZH2, and CREBBP are suggestive of epigenetic (chromatin regulating) drivers of transformation in some patients [40–42], while alterations in MYC or CDKN2A/B in other patient samples implicate