SHORT REPORT OPEN ACCESS

Treatment of an Indolent T-Cell Lymphoma of the Gastrointestinal Tract Harboring *STAT3::JAK2* With Jakafi (Ruxolitinib) With Significant Clinical Improvements

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ABSTRACT

Introduction: Indolent T-cell lymphoma of the gastrointestinal tract (ITCL-GI) is a rare primary T-cell lymphoma from the gastrointestinal (GI) tract, there has been no documented successful treatment at the present time.

Results: A CD4(+)/CD8(−) ITCL-GI with *STAT3::JAK2* fusion was treated with Jakafi (Ruxolitinib), which resulted in significant clinical improvements.

Conclusion: Next generation sequencing is highly recommended for any new diagnosis of CD4(+)/CD8(−) ITCL-GI in order to detect if *STAT3::JAK2* can be found in order to treat the patient with JAK2 inhibitor such as Jakafi (Ruxolitinib).

Clinical trial registration: The authors have confirmed clinical trial registration is not needed for this submission.

1 | Introduction

Indolent T-cell lymphoma of the gastrointestinal tract (ITCL-GI) is a rare clonal T-cell proliferation that presents unique diagnostic and therapeutic challenges. Recognized in the 5th edition of the World Health Organization (WHO) Classification of Hematolymphoid Tumors [1], ITCL-GI can mimic other gastrointestinal (GI) conditions, complicating accurate diagnosis; furthermore, there is no effective and optimal treatment for these patients although they have been treated with various regiments [2] but with little success. Identification of *STAT3::JAK2* in the majority of CD4+/CD8− ITCL-GI has opened new avenues for targeted therapies as demonstrated in cell culture and in animal model [3, 4]. Herein we report the first case of *STAT3::JAK2* harboring ITCL-GI, in which the patient was empirically and successfully treated with Jakfi (Ruxolitinib), a specific JAK2 inhibitor. Although the patient showed significant clinical improvement, there is little morphologic changes between the pre- and post-treatment biopsies, the possible reasons are discussed.

2 | Methods

2.1 | Case Report

The patient was a 56-year-old male with 1.5-year history of chronic diarrhea, decreased vitamin K levels, and unintentional approximately 50 pounds weight loss. The clinical suspicion at that time included microscopic colitis, celiac disease (despite the patient's Hispanic ethnicity), secretory diarrhea, or Whipple disease. During the period of 7 years from 2011–2018, he underwent six GI biopsies and one bone marrow biopsy, the latter of which showed no involvement by T-cell lymphoma; however, all of his six GI biopsies showed similar findings, in which the

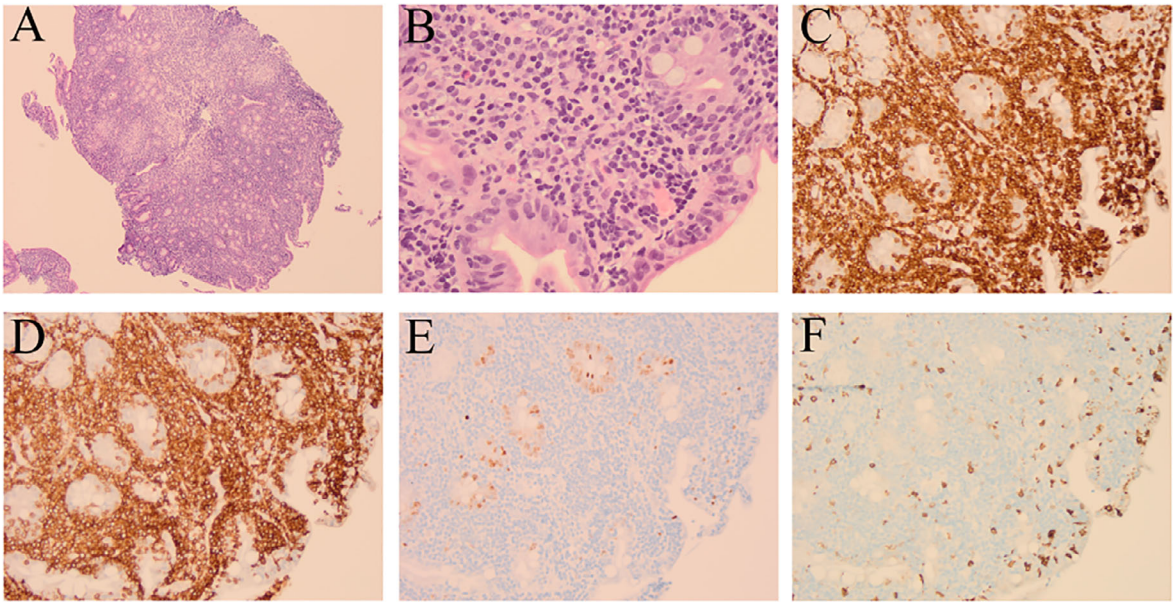

FIGURE 1 | **Composite microphotographs from duodenum biopsy performed in May 2017**. (A and B) The low- (A) and high-power magnifications of dense atypical small mature lymphoid infiltrate of lamina propria (the original magnifications of A and B are 40× and 400×, respectively); (C–F) the atypical lymphoid cells are diffusely and strongly positive for CD3 (C), CD4 (D), but negative for CD7 (E), or CD8 (F) (the original magnifications of C, D, E, and F are 200×, 200×, 200×, and 200×, respectively).

lamina propria was infiltrated by atypical small mature lymphoid cells without a significantly increased number of intraepithelial lymphocytes (IELs).

2.2 | Immunohistochemistry and Molecular Studies

By immunohistochemistry, the atypical lymphoid cells were positive for CD3, CD4, and CD5 but negative for CD7, CD8, CD56, EBV, TdT, or TIA-1 (Figure 1). Ki-67 was low (<5%). Other morphologic findings included presence of non-caseating granulomas (Figure 1). Molecular studies showed a monoclonal rearrangement of the T-cell receptor (TCR) gamma gene from his 1st duodenal biopsy in April 2011 and all of the subsequent GI biopsies. The patient underwent esophagogastroduodenoscopy (EGD) in July 2017 and found: (1) stomach appears diffusely edematous with erosions; (2) duodenal mucosa appears diffusely edematous and granular with flattened villi. With the advent of next generation sequencing (NGS), the patient was found to have *STAT3::JAK2* from his duodenum biopsy in July 2017. In addition, the patient has *MLL2* P4750fs*47 mutation. However, the patient had a stable microsatellite status with low tumor mutation burden at 2 Muts/Mb. Taken together, the patient has a CD4(+)/CD8(−) ITCL-GI with *STAT3::JAK2* according to the 5th edition of WHO Classification of Tumors-Haematolymphoid Tumors (1), although an enteropathy-associated T-cell lymphoma (EATL) with atypical immunophenotype was initially erroneously favored from the 1st (April 2011) biopsy.

3 | Results

As JAK2 is part of the balanced translocation, we postulated that a dysregulated JAK2 could be the target, thus the patient was treated with Ruxolitinib (also known as Jakafi) at a dose of 10 mg B.I.D starting December 2017. After 2 months of treatment with Jakafi, the patient reported improvement in his diarrhea. After 3 months' treatment, he stated that the diarrhea had almost resolved. Given the significant clinical improvement, we wanted to assess for any possible endoscopic and morphologic changes: to our surprise, there were similar EGD findings to those in July 2017, and there were no discernible histomorphologic changes from the GI biopsy performed in May 2018, namely, no morphologic or immunohistochemical changes (data not shown); at the molecular level, there was persistent monoclonal TCR rearrangement and continued presence of *STAT3::JAK2* fusion. The patient had, nevertheless, been on Jakafi treatment until he was infected with COVID-19 and died of pneumonia.

4 | Discussion

We present herein the first case, to the best of our knowledge, of *STAT3::JAK2* harboring CD4(+)/CD8(−) ITCL-GI with significantly improved clinical outcomes upon treatment with Jakafi, a Jak2 inhibitor. This case has the following unique characteristics. First, the patient's very 1st GI biopsy in April 2011 was incorrectly diagnosed mainly due to the fact that the formal recognition of ITCL-GI was not proposed until 2013, 2 years after the 1st biopsy [5]. This case also emphasized the need to distinguish ITCL-GI from other primary GI T-cell lymphomas as discussed in details in the author (Wang HY)'s recent review article [2]. Second, molecular studies especially NGS are always preferred whenever possible, as they may provide actionable targets for treatment. In fact, this is the seventh reported case of ITCL-GI with a *STAT3::JAK2* mutation in the English literature as of writing. Third, this is the first empirically treated case of ITCL-GI with Jakafi, a JAK2-specific inhibitor, although Jakafi has been used to treat *JAK2* mutated myeloproliferative neoplasms

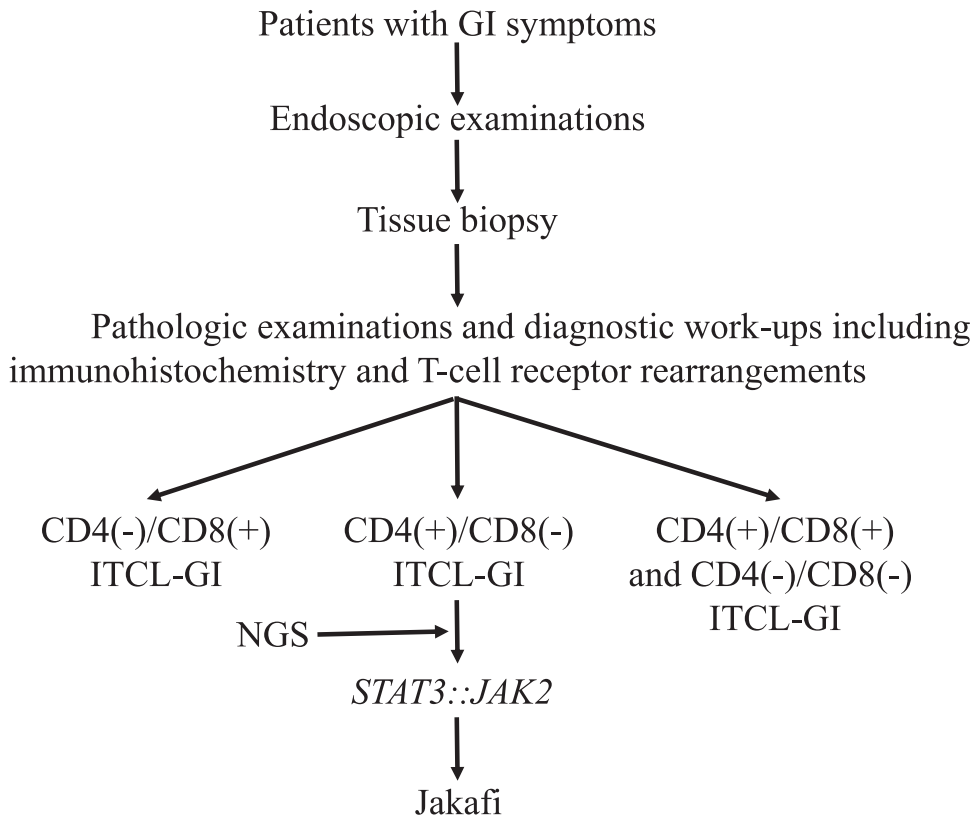

FIGURE 2 | Proposed work-flow for diagnosis and treatment of CD4(+)/CD8(−) ITCL-GI with *STAT3::JAK2*. ITCL-GI, indolent T-cell lymphoma of the gastrointestinal.

with track record of success for a long time [6]. Although our initial treatment of the patient with Jakafi was based on the presumed JAK2 translocation-driven pathogenic process, our speculation in December 2017 was later confirmed by in vitro and mouse model studies in 2020 [4], which showed that among five JAK2 inhibitors that demonstrated dose-dependent inhibition of *STAT3::JAK2*-expressing Ba/F3 cell growth, Jakafi had the most potent inhibitory effect [4].

It is of interest to point out that despite significant clinical and symptomatic improvements, there were no endoscopic nor histomorphologic changes in the post-Jakafi treated biopsied specimens after 6 months' treatment. This lack of endoscopic and histomorphologic improvements could be due to several possible reasons: suboptimal daily dosage and/or inadequate treatment duration, which highlight the very need for further large scale prospective clinical trials, although it will be challenging as such cases are indeed rare. On the basis of our reported case, we propose the following work-flow (Figure 2).

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

There are no further data available for this study.