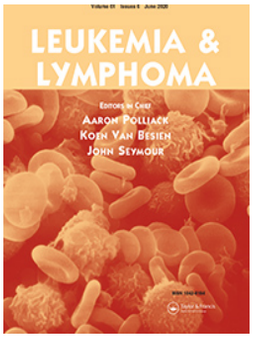

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ORIGINAL ARTICLE

A matched case-control study comparing features, treatment and outcomes between patients with non-IgM lymphoplasmacytic lymphoma and Waldenström macroglobulinemia

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ABSTRACT

Cases of non-IgM lymphoplasmacytic lymphoma (LPL) are rare. We performed a case–control study comparing features and outcomes of 31 non-IgM LPL cases and 93 Waldenström macroglobulinemia (WM) controls matched by age, sex, and year of diagnosis. Odds of *MYD88* mutations were lower (odds ratio (OR) 0.22, $p = .05$), and median time to treatment was shorter in cases than in controls (4 *vs.* 32 months; $p < .001$). Odds of extramedullary disease were higher (OR 4.20, $p = .01$), while odds of neuropathy (OR 0.22, $p = .25$), and hyperviscosity (OR 0.26, $p = .26$) were lower in cases than in controls. Odds of using chemoimmunotherapy were higher (OR 2.62, $p = .11$) while odds of using proteasome inhibitors (OR 0.35, $p = .15$) and BTK inhibitors (OR 0.17, $p = .21$) were lower in cases than in controls. There were no differences in response and overall survival (OS) between cases and controls. Despite clinicopathological differences, response, and survival outcomes are similar between non-IgM LPL cases and WM controls.

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Waldenstrom's macroglobulinaemia; lymphoplasmacytic lymphoma; response; survival; case–control study

Introduction

Lymphoplasmacytic lymphoma (LPL) is a rare indolent subtype of non-Hodgkin lymphoma. The estimated incidence of LPL in the United States is 1500–2000 cases per year [1]. A serum monoclonal IgM paraprotein is present in over 90–95% of patients with LPL and constitutes the condition widely known as Waldenström macroglobulinemia (WM) [2]. LPL cases secreting monoclonal immunoglobulins other than IgM (non-IgM LPL) are exceedingly rare. There are very few case series on non-IgM LPL patients [3–6] and little is known about the clinical characteristics and outcomes of patients with non-IgM LPL.

We designed a matched case–control study to evaluate the clinical and pathological characteristics of non-IgM LPL cases in comparison with matched WM controls. Additional metrics of interest include time to first treatment, indications to treat, first-line treatment, and response, as well as time to next treatment (TTNT), survival after first-line treatment initiation (SAFTI), and overall survival (OS).

Patients and methods

Cases and controls

We identified cases of non-IgM LPL from the records of the Bing Center for Waldenström Macroglobulinemia (BCWM) at the Dana-Farber Cancer Institute (DFCI) in Boston, MA, which were diagnosed and/or treated between 2000 and 2018. We included cases with pathologically confirmed diagnosis and complete survival data. Three WM controls per each non-IgM LPL case were selected from the records of the BCWM and were matched for age (±1 year), sex and year of diagnosis (±1 year). If more than three controls were encountered in the records, three controls were selected in a random fashion. All cases and controls signed consent to have their data collected for research

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purposes. All bone marrow biopsy slides from cases and controls were reviewed at DFCI.

Data gathering

Pertinent data were gathered retrospectively and included pathological characteristics at diagnosis, clinical characteristics at therapy initiation, presence of extramedullary disease, *MYD88* and *CXCR4* mutational status, time to first treatment initiation, therapy administered, best response, TTNT, SAFTI, and OS. Extramedullary disease was defined as lymphadenopathy $\geq$1.5 cm in diameter, splenomegaly $\geq$15 cm in the largest axis and/or involvement of other extranodal sites (e.g. pleura, kidney, etc.). Bone marrow involvement was defined as the percentage of infiltration of the intertrabecular space by LPL. Responses for WM controls and immunoglobulin secreting LPL cases were defined per criteria from the sixth IWWM [7]. For non-secretory LPL cases, as there are no standard criteria, response was assessed by the percentage of bone marrow involvement: progressive disease was defined as >25% increase, stable disease as <25% increase or decrease, minor response as $\geq$25% but <50% decrease, partial response as $\geq$50% but <90% decrease, very good partial response as $\geq$90% but no complete resolution, and complete response as complete resolution of bone marrow involvement. TTNT was defined as the time between frontline treatment initiation and second treatment initiation. SAFTI was defined as the time between frontline treatment initiation and death or last follow-up. OS was defined as the time between WM diagnosis and death or last follow-up. *MYD88* and *CXCR4* mutational status was assessed using allele-specific polymerase chain reaction (PCR) for *MYD88* L265P and nonsense *CXCR4* mutations. Frameshift *CXCR4* mutations were assessed by Sanger sequencing. *MYD88* and *CXCR4* mutational detection techniques have been previously reported [8–11].

Statistical analysis

Patients' characteristics are presented using descriptive statistics. We assessed categorical differences between groups using the Fisher exact test (2-sided). The association measures are reported using odds ratio (OR) with 95% confidence interval (CI). Time to first treatment, TTNT, SAFTI, and OS curves were estimated using the Kaplan–Meier method for incomplete observations. Differences on survival distributions between cases and controls were assessed using the long-rank test and Cox proportional-hazard regression models. Survival outcomes are reported as hazard ratio (HR) and 95% CI. p Values <.05 were considered statistically significant. Calculations were obtained using STATA 15 (StataCorp, College Station, TX).

Results

Baseline characteristics

Thirty-one non-IgM LPL cases and 93 WM controls were included in the final analysis. In non-IgM LPL cases, median age at diagnosis was 63 years (range 37–83 years), 12 cases (39%) were male, and 22 (58%) were diagnosed after 1 January 2010. For WM controls, median age at diagnosis was 63 years (range 37–84 years), 36 were male (39%), and 66 (58%) were diagnosed after 1 January 2010. From the 31 non-IgM LPL cases, 20 cases (65%) were IgG, 5 (16%) were IgA, 2 (6%) were light-chain (LC; 1 kappa and 1 lambda restricted) and 4 (13%) were non-secretory (NS). Bone marrow involvement was not different between non-IgM LPL cases (median 60%, range 5–95%) and WM controls (median 60%, range 5–95%). Flow cytometry studies from bone marrow aspirate material showed positive expression of CD20 and CD19 in 100% of non-IgM LPL cases and WM controls. Among non-IgM LPL cases, there was positive (subset and/or dim) expression of CD5 in 4 cases (13%), and there was partial positive expression of CD23 in 7 cases (29%). There was positive expression of CD5 and CD23 in 14 (15%) and 18 (19%) WM controls, respectively. None of the non-IgM LPL cases had a positive expression of CD10, while eight (9%) WM controls had positive expression of CD10. None of the 14 cases and 52 controls tested expressed cyclin D1. There were no statistically significant differences in rates of CD5, CD10, CD23 and cyclin D1 expression between cases and controls. The *MYD88 L265P* mutation was detected in 16 of 20 non-IgM LPL cases (80%) and in 88 of 93 (95%) of WM controls tested (OR 0.22, 95% CI 0.04–1.30; $p = .05$). *CXCR4* mutations were detected in 5 of 20 non-IgM LPL cases (25%) and 35 of 93 WM controls (38%) tested (OR 0.55, 95% CI 0.14–1.79; $p = 0.32$).

Characteristics at treatment initiation

At the time of this report, 22 (71%) non-IgM LPL cases and 45 (48%) WM controls have started therapy. The median time from diagnosis to treatment initiation for non-IgM LPL cases was 4 months (95% CI 1–11 months) and for WM controls was 32 months (95% CI 22-not reached). The odds for treatment

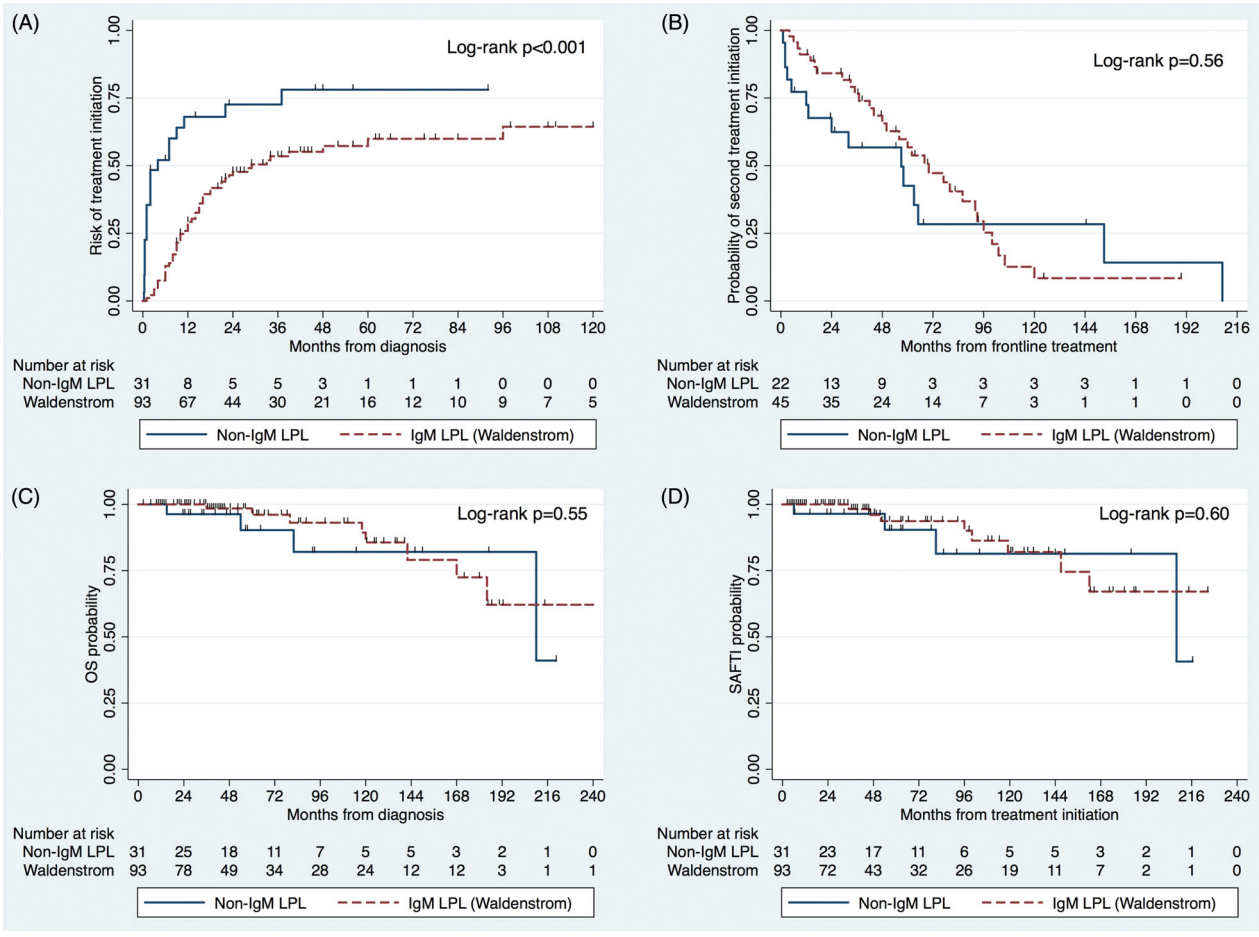

Figure 1. Estimated Kaplan–Meier curves for (A) time from diagnosis to first treatment initiation; (B) time from first treatment to second treatment initiation; (C) overall survival probability; and (D) survival after first line treatment initiation in 31 non-IgM LPL cases and 93 WM matched controls.

initiation was three times higher for non-IgM LPL cases than for WM controls (OR 3.10, 95% CI 1.85–5.20; $p < .001$; Figure 1(A)). At treatment initiation, non-IgM LPL cases had median serum IgG and serum IgA levels at the time of treatment initiation was 3,967 mg/dl (range, 804–8006 mg/dl) and 1980 mg/dl (range, 1020–6210 mg/dl), respectively. Median hemoglobin level was 11.3 g/dl (range 7.7–14.7 g/dl) and median platelet count was 224 K/ul (range, 109–411 K/ul). At treatment initiation, WM controls had median serum IgM level of 4231 mg/dl (range 211–6123 mg/dl), median hemoglobin level of 10.9 g/dl (range 6.8–14.5 g/dl) and median platelet count 196 K/ul (95–405 K/ul). There were no detectable differences in hemoglobin level or platelet count between non-IgM cases and WM control.

Indications to treat in both non-IgM LPL cases and WM controls are shown in Table 1. The most common indications to treat in both non-IgM LPL cases and WM controls were symptomatic anemia and extramedullary disease. The odds of symptomatic extramedullary disease were statistically higher in cases than in controls (55% *vs.* 22%; $p = .01$). The odds of neuropathy and symptomatic hyperviscosity were lower in non-IgM LPL cases than in WM controls, but the differences were not statistically significant. The non-IgM LPL case with neuropathy was non-secretory (later on suspected to be unrelated to underlying LPL)

Table 1. Indications to treat in non-IgM LPL cases and WM controls at the time of treatment initiation.

	Non-IgM LPL ($n = 22$)	WM ($n = 45$)	OR (95% CI)	p
Symptomatic anemia	11 (50%)	25 (55%)	0.80 (0.25–2.51)	.80
Extramedullary disease	12 (55%)	10 (22%)	4.20 (1.23–14.4)	.01
Lymphadenopathy	7 (32%)	6 (13%)	3.03 (0.73–12.7)	.10
Splenomegaly	3 (14%)	3 (7%)	2.21 (0.27–17.8)	.39
Other extranodal sites*	7 (32%)	5 (11%)	3.73 (1.07–13.0)	.04
Neuropathy	1 (5%)	8 (18%)	0.22 (0.00–1.87)	.25
Hyperviscosity	1 (5%)	7 (16%)	0.26 (0.01–2.28)	.26

LPL: lymphoplasmacytic lymphoma; OR: odds ratio; CI: confidence interval; WM: Waldenström macroglobulinemia.
*Other sites of extranodal involvement included kidney ($n = 2$ non-IgM LPL, $n = 3$ WM), pleural effusion ($n = 1$ non-IgM LPL; $n = 2$ WM), duodenum ($n = 2$ non-IgM LPL), cardiac ($n = 1$ non-IgM LPL) and bone ($n = 1$ non-IgM LPL).

Table 2. Frontline treatment and response to therapy in non-IgM LPL cases and WM controls at the time of treatment initiation.

	Non-IgM LPL ($n = 22$)	WM ($n = 45$)	OR (95% CI)	p
Frontline treatment				
Chemoimmunotherapy	13 (59%)	16 (36%)	2.62 (0.82–8.54)	.11
Proteasome inhibitors	3 (14%)	14 (31%)	0.35 (0.06–1.51)	.15
BTK inhibitors	1 (4%)	10 (22%)	0.17 (0.00–1.35)	.09
Single agent rituximab	4 (18%)	3 (7%)	3.04 (0.45–22.5)	.21
Other agents*	1 (4%)	2 (4%)	1.02 (0.02–20.7)	1.00
Response to frontline				
CR/VGPR	4 (18%)	10 (22%)	0.78 (0.16–3.21)	1.00
PR	11 (50%)	24 (53%)	0.88 (0.28–2.75)	1.00
MR	4 (18%)	7 (16%)	1.21 (0.23–5.48)	1.00
SD/PD	3 (14%)	4 (9%)	1.62 (0.21–10.5)	.68

LPL: lymphoplasmacytic lymphoma; OR: odds ratio; CI: confidence interval; BTK: Bruton tyrosine kinase; CR: complete response; VGPR: very good partial response; PR: partial response; MR: minor response; SD: stable disease; PD: progressive disease; WM: Waldenström macroglobulinemia.
*Other agents include immunomodulating agents ($n = 1$ non-IgM LPL, $n = 1$ WM) and everolimus ($n = 1$ WM).

and the case with hyperviscosity was an IgA LPL case with serum IgA level at 4000 mg/dl. There was no difference in the odds of symptomatic anemia between cases and controls.

Frontline treatment, response rate, and time to next treatment

The regimens used for frontline treatment of non-IgM LPL cases and WM controls as well as the categorical response rates to these regimens are shown in Table 2. The odds of using chemoimmunotherapy and single agent rituximab were higher in non-IgM LPL cases than in WM controls, although the differences were not statistically significant. The odds of using proteasome inhibitors and BTK inhibitors were statistically lower in non-IgM LPL cases than in WM controls, with a trend toward statistical significance on the use of BTK inhibitors. As previously reported, the one non-IgM LPL case treated with ibrutinib carried MYD88 L265P but CXCR4 mutations were not detected [12]. There were no differences in categorical responses to frontline therapy between cases and controls. Also, there were no differences in categorical responses based on each individual treatment regimen (data not shown). Fifteen non-IgM LPL cases and 30 WM controls have received a second treatment. The median TTNT for non-IgM LPL cases was 57 months (95% CI 12–153 months) and for WM controls was 70 months (95% CI 48–92 months), with an HR of second treatment initiation of 1.21 (95% CI 0.63–2.30; $p = .57$) for cases when compared with controls (Figure 1(B)).

Survival analysis

With a median follow-up time of 56 months (95% CI 34–92 months) and 55 months (95% CI 34–92 months), there were 4 (13%) and 8 (9%) deaths in non-IgM LPL cases and WM controls, respectively. The 5- and 10-year OS rates for non-IgM LPL cases were 90% (95% CI 65–98%) and 82% (95% CI 52–94%), respectively. The 5- and 10-year OS rates for WM controls were 96% (95% CI 85–99%) and 86% (95% CI 68–94%), respectively (Figure 1(C)), with an HR for OS of 1.45 (95% CI 0.43–4.94; $p = .55$) for cases when compared with controls.

The 5- and 10-year SAFTI rates for non-IgM LPL cases were 90% (95% CI 65–98%) and 81% (95% CI 50–94%), respectively. The 5- and 10-year SAFTI rates for WM controls were 94% (95% CI 81–98%) and 82% (95% CI 63–92%), respectively (Figure 1(D)), with an HR for SAFTI of 1.37 (95% CI 0.41–4.67; $p = .61$) for cases when compared with controls.

Discussion

We carried a retrospective case–control study to better understand the clinical features, diagnosis, pathology, indications to treat, treatment modalities, response to therapy as well as PFS, SAFTI and OS in patients with non-IgM LPL, and compared these characteristics and outcomes with patients with WM. To maximize the quality of our observations and minimize confounding, we included consecutive non-IgM LPL cases and matched them with WM controls selected from the same database by age at diagnosis, sex and year of diagnosis. Also, both cases and controls were pathologically confirmed.

Our study shows that in non-IgM LPL patients, IgG is the most common subtype, followed by IgA, non-secretory, and light chain LPL. These findings are consistent with prior reports [4,5]. Pathologically, the expression of CD19 and CD20 is universally positive and the proportion of cases expressing CD5, CD10, CD23 appears similar to WM. None of the cases or controls tested expressed cyclin D1. The odds of harboring *MYD88 L265P* and *CXCR4* mutations were lower in non-IgM LPL cases than in WM controls. There was a statistical trend for *MYD88* but there was no statistical significance for *CXCR4* mutations. Our study supports the prevalence and relevance of *MYD88* and *CXCR4* mutations in non-IgM LPL, which can have diagnostic implications. In patients with a non-IgM paraprotein, multiple myeloma would be the most prevalent underlying malignancy. The presence of *MYD88* and/or *CXCR4* mutations in a patient with a

non-IgM paraprotein would strongly support a diagnosis of LPL over multiple myeloma, as *MYD88* or *CXCR4* mutations have not been detected in multiple myeloma [13–15]. The rates of *MYD88* and *CXCR4* mutations are higher than previously reported, which might be in part due to the additional selection of CD19-positive cells prior to PCR and Sanger sequencing performed in our research laboratory. We had previously shown that cell selection in bone marrow aspirate samples increases the sensitivity of *MYD88* and *CXCR4* mutation detection, when compared with non-selected samples [16].

With regard to treatment initiation, there was a significantly shorter median time to first treatment in non-IgM LPL cases when compared with WM controls. It is possible that despite our efforts for appropriately matching cases and controls, selection bias could have been introduced. However, the median time to treatment of 4 months seen in non-IgM LPL cases is similar to the previously reported 6 months in a recent Italian study [5]. In that same study, the time to treatment in WM patients was 71 months. Additionally, in a recent study on asymptomatic WM patients, the median time to frontline treatment initiation was 3.9 years [17], which is marginally longer than the 32 months presented here. Overall, the mounting evidence supports non-IgM LPL patients having a shorter time to treatment initiation from diagnosis than WM patients. This difference could be in part explained by the lower rates of *MYD88 L265P* mutations seen in non-IgM LPL cases, as *MYD88* wild type mutational status was associated with shorter time to treatment initiation in a recent study from our group [17].

There were differences on the indications to treat between non-IgM LPL cases and WM controls. Non-IgM LPL cases appeared to have statistically significant higher odds of extramedullary disease than WM controls. This finding is consistent across the few case series reported to date [3–6], arguing against selection bias. It is therefore likely that the higher rate of extramedullary disease on cases than in controls could be explained by a distinct underlying pathophysiology. Also, there were lower rates of neuropathy and symptomatic hyperviscosity in non-IgM LPL cases than in WM controls, which is consistent with a prior report [3]. These differences, in our opinion, are more likely related to the physicochemical properties of IgM. Peripheral neuropathy tends to affect 20–25% of patients with WM and is typically demyelinating, distal, sensory, bilateral, and slowly progressing [18]. A proportion of WM patients with IgM-mediated peripheral neuropathy have anti-myelin associated glycoprotein (MAG) antibodies, which are an important pathophysiological factor in the development of neuropathy. Anti-MAG antibodies have not been associated with IgG or IgA paraproteins. Symptomatic hyperviscosity occurs in 10–15% of WM patients and seems to have a non-linear relation with serum IgM levels [19]. The higher rates of hyperviscosity in WM than in non-IgM LPL can be explained by the molecular weight of the secreted immunoglobulins. The molecular weight of IgM at 900 kilodaltons is higher than that of IgG (150 kilodaltons) or IgA (178 kilodaltons) [20], therefore higher serum levels of IgG or IgA than IgM would be needed to promote an increase in serum viscosity.

There were detectable differences on the frontline treatment regimens used between non-IgM LPL cases and WM controls. It is important to note that the treatment of non-IgM LPL is not standardized and, given the limited data available, the treatment of non-IgM LPL should mimic the treatment of WM, as recommended by the National Comprehensive Cancer Network [21]. There were higher odds of using alkylating agents and lower odds of using proteasome inhibitors and BTK inhibitors in cases than in controls. This difference could be associated with the clinical presentation of non-IgM LPL cases with higher rates of extramedullary disease, such as lymphadenopathy and organomegaly, which could be perceived as "lymphomatous." It is possible than, in this scenario, practitioners would favor alkylating agents over targeted agents, although additional research is needed to clarify this point. We also must acknowledge that the treatment for non-IgM LPL and WM has evolved over the last decades and this could have introduced bias in our analysis, and, therefore, our results should be taken with caution. The response rates to frontline treatment and the median TTNT did not seem to statistically differ between cases and controls. There were no detectable differences on median follow-up, SAFTI and OS times between non-IgM LPL cases and WM controls. Also, there were no detectable differences on 5- and 10-year SAFTI and OS rates between cases and controls. We had previously reported durable response to single agent ibrutinib in a heavily pretreated patient with non-IgM LPL who carried the *MYD88 L265P* mutation and did not carry a *CXCR4* mutation [12]. One could advocate for the use of BTK inhibitors as well as *MYD88* and *CXCR4* mutational testing in non-IgM LPL patients.

In conclusion, our study supports that non-IgM LPL patients present with similar features (though with lower odds of neuropathy and hyperviscosity) than

WM patients and should be treated in a similar fashion and that deep and durable responses are to be expected. Finally, the survival rates in non-IgM LPL patients did not appear different than WM counterparts. We believe our findings add to the existing body of literature on non-IgM LPL providing practitioners with insights that could guide diagnostic approaches, treatment decisions and prognostic discussion with patients affected by this rare condition and their family members.

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Author contributions

JJC designed the study and performed the analysis. JJC, GI and JNG gathered patients' data. MGD, MLG, AKo, CJ, XL, MM, NT, CJP, LX, GY and ZRH performed molecular testing in patients' samples. JJC, CAF and SPT took care of patients. JJC and JNG drafted the manuscript. All authors critically reviewed and approved the final manuscript.

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