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ORIGINAL ARTICLE

t(11;18)(q21;q21) translocation as predictive marker for non-responsiveness to salvage thalidomide therapy in patients with marginal zone B-cell lymphoma with gastric involvement

Sung-Hsin Kuo · Ann-Lii Cheng · Chung-Wu Lin · Chih-Hung Hsu · Ming-Shiang Wu · Kun-Huei Yeh · Yi-Shin Tzeng · Li-Tzong Chen

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Abstract
Purpose Activation of TNF-α/NF-κB-related signaling pathway is crucial in sustain the growth of *Helicobacter pylori*-independent gastric mucosa-associated lymphoid tissue type (MALT) lymphoma. Thalidomide is an anti-angiogenic agent with anti-TNF-α and anti-NF-κB activity. This retrospective study evaluated the efficacy of thalidomide in standard therapy-failure gastric MALT lymphoma.

Methods Between October 2003 and September 2007, 10 patients with antibiotics-resistant, chemotherapy-refractory gastric MALT lymphoma who received salvage thalidomide therapy at daily doses of 100–200 mg were identified from medical records and included. Status of t(11;18)(q21;q21) was determined by reverse transcriptase polymerase chain reaction for API2-MALT1 transcript, while expression of NF-κB was detected by immunohistochemistry. Tumor response was evaluated by RECIST criteria.

Results Tumors were of stage IV in seven and IE/IIE-1 in three. The best tumor response after thalidomide was complete response in two and partial in three, with an overall response rate of 50% (95% confidence interval, 12.3–87.7%). At median follow-up of 39.3 months, the 3-year event-free and overall survival rates were 36.0% and 85.7%, respectively. API2-MALT1 transcript was detected in four (40%) tumors. Objective response rates of tumors with and without t(11;18)(q21;q21) were 0% (0/4) and 83% (5/6), respectively, $P = 0.048$ (Fisher's exact test). Thalidomide treatment was associated with significant down-regulation of nuclear NF-κB expression levels in residual neoplastic cells and microenvironments of responsive tumors, but not in t(11;18)(q21;q21)-positive, thalidomide-refractory tumors.

Conclusions Thalidomide is an effective salvage treatment for standard therapy-failure, t(11;18)(q21;q21) translocation-negative gastric MALT lymphoma and deserves further exploration.

Keywords NF-κB · Thalidomide · Stomach · API2-MALT1 · MALT lymphoma

Abbreviations

MALT	Mucosa-associated lymphoid tissue
RT-PCR	Reverse transcriptase polymerase chain reaction
CR	Complete remission

S.-H. Kuo · A.-L. Cheng · C.-H. Hsu · K.-H. Yeh · Y.-S. Tzeng
Department of Oncology, National Taiwan University Hospital and National Taiwan University College of Medicine, Taipei, Taiwan

S.-H. Kuo · A.-L. Cheng · M.-S. Wu
Department of Internal Medicine, National Taiwan University Hospital and National Taiwan University College of Medicine, Taipei, Taiwan

C.-W. Lin
Department of Pathology, National Taiwan University Hospital and National Taiwan University College of Medicine, Taipei, Taiwan

S.-H. Kuo · A.-L. Cheng · C.-H. Hsu · K.-H. Yeh · Y.-S. Tzeng
Cancer Research Center, National Taiwan University College of Medicine, Taipei, Taiwan

A.-L. Cheng · L.-T. Chen (✉)
National Institute of Cancer Research, National Health Research Institutes, 2F. No.36, Sheng-Li Rd, Tainan 70456, Taiwan
e-mail: leochen@nhri.org.tw

L.-T. Chen
Department of Internal Medicine, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan

L.-T. Chen
Department of Internal Medicine,
National Cheng-Kung University Hospital, Tainan, Taiwan

PR Partial remission
SD Stable disease
PD Disease progression
MVD Microvascular density

Introduction

Gastric mucosa-associated lymphoid tissue (MALT) lymphoma is the most common type of MALT lymphoma and characterized by its close association with *Helicobacter pylori* (*H. pylori*) infection [1, 2]. *H. pylori* eradication therapy is effective in 60–80% of early-stage, *H. pylori*-positive gastric MALT lymphoma, but much less effective in *H. pylori*-negative, translocation-positive and/or advanced-stage tumors [2, 3]. For those *H. pylori*-independent tumors, despite potential long-term side effects of gastric function abnormalities [4–6], surgery and radiotherapy are the favorable treatment options for localized gastric MALT lymphoma because of excellent local disease control. On the other hand, systemic chemotherapy either alone or in combination with anti-CD-20 monoclonal antibodies immunotherapy is a favorable option for palliation of symptomatic, disseminated MALT lymphoma [2–4]. However, chemotherapy for advanced MALT lymphoma is non-curative and tumor relapse is generally inevitable, as it does for other categories of indolent lymphoma.

Our previous studies showed that, regardless the status of t(11;18)(q21;q21) translocation, nuclear expression of BCL10 and/or NF-κB is highly predictive for loss of *H. pylori* dependence of gastric MALT lymphoma [3, 7–9], and activation of tumor necrosis factor alpha (TNF-α) signals may recapitulate the scenario of nuclear translocation of both NF-κB and BCL10 in tumor cells [10, 11]. These observations suggest the presence of aberrantly activated TNF-α-related pathway within either microenvironment or tumor cells per se may sustain the growth and attribute to the *H. pylori*-independent transformation of gastric MALT lymphoma cells.

Thalidomide, a notoriously teratogenic agent, has recently been shown to exhibit potent anti-inflammatory, anti-angiogenic, and immunomodulatory activity and to be clinically active in patients with refractory multiple myeloma, myelofibrosis with myeloid metaplasia, and mantle cell lymphoma [12–14]. Although mechanisms underlying the effectiveness of thalidomide in hematologic malignancies are not well elucidated, recent data suggest its activity may be attributed to inhibition of multiple targets in the TNF-α/NF-κB signaling pathway in certain immune and malignant cells [15–17]. Therefore, thalidomide appears to be a reasonable candidate for salvage treatment of gastric MALT lymphoma refractory or resistant to standard therapy. However, the efficacy of thalidomide for *H. pylori*-independent gastric MALT lymphoma remains inconclusive.

Methods

Patients, treatment, and tumor evaluation

We identified and reviewed the medical records and histopathologic materials of patients diagnosed with extra-nodal marginal zone B-cell lymphoma of the stomach during the period October 2003 to September 2007. The diagnosis of MALT lymphoma was made according to the criteria described by Isaacson and Chan et al. [1, 18] and characterized by the presence of low-grade centrocyte-like cell infiltrates and lymphoepithelial lesions. Those with features of high-grade transformation, namely, confluent clusters or sheets of large cells resembling centroblasts or lymphoblasts, were excluded from the study. A total of 10 patients (seven men, three women; median age, 61 years [range, 48–78 years]) with histologically confirmed gastric MALT lymphoma that had failed to *H. pylori* eradication therapy and/or at least one line of chemotherapy, and received salvage thalidomide therapy was identified and included into the study. Institutional Review Board of National Taiwan University Hospital and Department of Health, Executive Yuen, Taiwan had approved the compassionate use of thalidomide for each patient.

Evaluation

All patients had standard staging work-up for gastric MALT lymphoma before the start of thalidomide treatment, including detailed physical examination and history review, hemogram with leukocyte differential count, serum lactate dehydrogenase (LDH) level, computed tomography (CT) of the chest, abdomen and pelvis, bone marrow aspiration and biopsy, and upper gastrointestinal endoscopic examination. Staging was based on Musshoff's modification of the Ann Arbor staging system. Follow-up CT examinations and endoscopic examination with biopsy of any suspicious lesion (for patients with gastric involvement) were performed every 2–3 months to assess response. Tumor response was evaluated according to RECIST criteria, but all specimens from certain biopsy session had to have a Wotherspoon's score $\leq$2 to document histological complete remission of lesions within the stomach.

Histology and immunohistochemistry

The expression status of NF-κB within MALT lymphoma tissue was detected by immunohistochemical (IHC) staining using anti-p65 antibody (sc-7151, Santa Cruz Biotechnology, Santa Cruz, CA). Nuclear expression of NF-κB was considered positive when nuclear staining of respective protein was detected in less than 10% of tumor cells [19, 20]. Reactive spleen and lymph node tissue sections

were used as controls. In addition, for the known immunemodulation and anti-angiogenesis properties of thalidomide, the changes of infiltrating inflammatory cells, including neutrophils, eosinophils and CD3-positive T cells (detected by anti-CD3 antibody, Dako SA, Glostrup, Denmark), and microvascular density (detected by anti-CD34 antibody, Dako SA, Glostrup, Denmark) within the microenvironment of paired tissue specimens, before and after thalidomide treatment, were carefully re-evaluated by one of the authors, CW Lin. The evaluation of CD34-positive microvascular density (MVD) was made according to the method described by Mazur and Alshenawy et al. [21, 22]. The analysis of MVD was performed as follows: the presence of a vessel lumen was not necessary for a structure to be defined as a microvessel. Three areas of maximal MVD (so-called hot spots) were identified by scanning slides in the light microscope at ×40 magnification. In each hot spot, microvessels (capillaries and small venules) were counted at ×400 magnification (each field representing an area of 0.375 mm^2). The mean number of microvessels from these 3 areas per 0.375 mm^2 was calculated as MVD [21, 22]. All IHC were performed on paraffin-embedded tissue sections using an indirect immunoperoxidase method according to the manufacturer's instructions.

Multiplex reverse transcriptase polymerase chain reaction for API2-MALT1 transcript

Total cellular RNA was extracted from formalin-fixed, paraffin-embedded tissues using an Ambion RNA isolation kit (AMS Biotechnology, Oxon, UK) and analyzed for API2-MALT1 fusion transcripts using multiplex RT-PCR as described previously [23]. Gastric MALT lymphoma samples known to possess API2-MALT1 fusion transcripts were used as a positive control. Where indicated, PCR products of the API2-MALT1 transcript were either directly sequenced or cloned into a vector (TOPO TA Cloning Kit; Invitrogen, Paisely, UK), sequenced with vector primers using dye-labeled terminators (BigDye Terminators; Applied Biosystems, Foster City, CA), and analyzed on a DNA sequencer (Model 310; Applied Biosystems).

Statistical analysis

Fisher's exact test was used to analyze the correlation between thalidomide response and presence of the t(11;18)(q21;q21) translocation. Student's *t* test or Mann–Whitney *U* test was used to evaluate the difference in the distribution of neutrophils, eosinophils, CD3-positive T cell cell counts, and CD34-positive MVD between thalidomide responsive tumors and thalidomide non-responsive tumors. The cut-off date for survival analysis was April 30, 2009. Event-free survival (EFS) was calculated from date of initial treatment until disease progression, relapse, discontinuation of treatment for any reason, or death [24]. Overall survival (OS) was calculated from date of initial treatment to date of death as a result of any cause [24]. Survival was estimated by the Kaplan–Meier method. All statistical analyses were performed on a personal computer with statistical package SPSS for Windows (Version 15.0, SPSS, Chicago, IL).

Table 1 Characteristics and thalidomide responses of patients and tumor expression of NF-κB and API2-MALT1 ($N = 10$)

Case	Age	Sex	Stage*	Extranodal involvement	Prior treatment	Thalidomide response	Regimen after thalidomide	Nuclear NF-κB expression	t(11;18)
1	54	M	IIE1/IV	Stomach, Waldeyer's ring, bone marrow	HPET, Chlorambucil	CR	R-COP	+	−
2	59	F	IV	Stomach, bone marrow	HPET	PR	Nil	+	−
3	78	M	IIE1	Stomach	HPET	PR	Nil	+	−
4	65	M	IV	Stomach, lung, bone marrow	Chlorambucil, CHOP	SD	Rituximab	+	+
5	63	M	IV	Stomach, lung	CP, R-PACE	PD	CP	+	+
6	53	F	IE/IV	Stomach, soft tissue	HPET	CR	Nil	+	−
7	65	M	IIE1	Stomach	HPET CHOP	PR	CP	+	−
8	74	F	IV	Stomach, parotid gland, bone marrow	CHOP	PD	R-GP	+	+
9	53	M	IE	Stomach	HPET Chlorambucil	SD	R-COP	+	+
10	48	M	IE/IV	Stomach, lung	HPET, CP, R	SD	Prednisolone	−	−

M male, *F* female, *HPET H. pylori* eradication therapy, *CR* complete remission, *PR* partial remission, *SD* stable disease, *PD* progression, *CHOP* cyclophosphamide, doxorubicin, vincristine, and prednisolone, *CP* chlorambucil and prednisolone, *R* rituximab, *PACE* prednisolone, doxorubicin, cyclophosphamide, and etoposide, *COP* cyclophosphamide, vincristine, and prednisolone, *GP* gemcitabine and etoposide, *Nil* no other treatments, *C* cytoplasmic, *n/c* both nuclear and cytoplasmic, + positive, − negative, *t(11;18)* API2-MALT1 transcript

* At diagnosis/before thalidomide

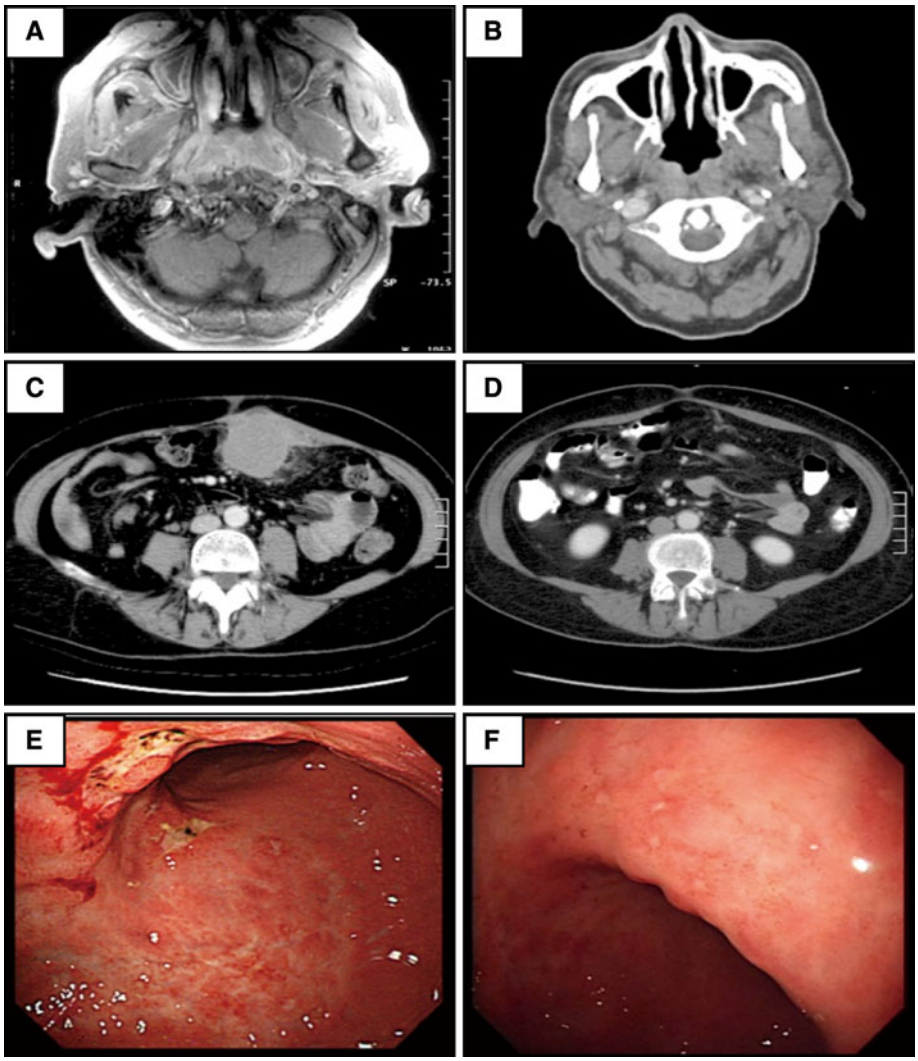


Fig. 1 Examples of gastric MALT lymphoma responsive to thalidomide. **a** before treatment, a prominent soft tissue lesions in the nasopharynx by magnetic resonance image in case #1, **b** which showed complete regression after thalidomide treatment by computed tomography (CT scan), **c** before treatment, a homogeneous soft tissue mass at the omentum near the umbilicus by CT scan in case #6, **d** which showed complete regression after thalidomide treatment; **e** before treatment, geographic ulcerations at the posterior wall of gastric angularis in endoscopic examination in case #7, **f** which showed significant regression with wide-base whitish scar in gross and residual lymphoma cells in histology after 6 months of thalidomide treatment

Results

Patients, treatment, and clinical outcome

Clinicopathologic features and prior treatments for each patient are summarized in Table 1 and Fig. 1. Of the 10 MALT lymphoma patients, tumor stage before thalidomide treatment was stage IE in one, IIE1 in two, and IV in seven. Among them, all seven patients with *H. pylori* infection at initial diagnosis had prior antibiotic treatment and documented cure of *H. pylori* infection before beginning thalidomide therapy. Of them, five had salvage chemotherapy and/or immunotherapy after antibiotic treatment failure including oral chlorambucil/prednisolone in three (cases #1, #9 and #10), CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone) chemotherapy, and rituximab monotherapy in case #7 and #10, respectively. Of the three patients (cases #4, #5, and #8) with initially *H. pylori*-negative stage IV MALT lymphoma, two had prior oral chlorambucil/prednisolone followed by either CHOP or R-PACE (rituximab, prednisolone, doxorubicin, cyclophosphamide, and etoposide); while the remaining patient had failed CHOP before beginning thalidomide.

Tumor response, progression-free survival, and overall survival

All 10 patients received 100–200 mg/day oral thalidomide. Best tumor response by RECIST criteria was complete response (CR) in two patients and partial response (PR) in three patients. The overall response rate (ORR) was 50% (95% confidence interval [CI], 12.3–87.7%) for all patients, and 67% (two of three) and 43% (three of seven) for patients with localized (stage I–IIE1) and advanced (stage IIE2–IV) MALT lymphoma, respectively. Median time from thalidomide therapy to best tumor response was 5.2 months (range, 4.0–5.9 months). Of the two patients with CR, one (case #6) remains disease free at 3.8 years after CR, while the other patient (case #1) had bone marrow relapse 2.2 years after thalidomide treatment but achieved

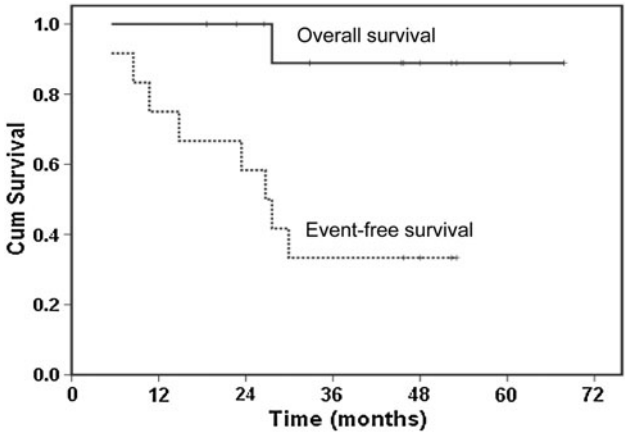


Fig. 2 Event-free survival (EFS) and overall survival (OS) in ten consecutive gastric MALT lymphoma patients who received salvage thalidomide after failure of *H. pylori* eradication therapy and standard chemotherapy

another CR with R-COP (rituximab, cyclophosphamide, vincristine, and prednisolone) therapy. Most of the patients with PR or stable disease had disease progression within 2 years after thalidomide treatment (Table 1). At a median follow-up of 39.3 months (range, 18.6–67.8 months), the 3-year event-free survival and overall survival were 36.0% and 85.7%, respectively (Fig. 2).

API2-MALT1 fusion transcript of t(11;18)(q21;q21)

The API2-MALT1 fusion transcript was detected in four (40%) tumors (Table 1). Of tumors with and without t(11;18)(q21;q21) translocation, the objective tumor response rate after thalidomide treatment was 0% (0/4) and 83% (5/6), respectively ($P = 0.048$, Fisher's exact test).

Expression of nuclear NF-κB

As shown in Table 1, the expression of nuclear NF-κB was detected in 9 of baseline tumor tissues. The expressions of NF-κB within either tumor cells or microenvironment was significantly down-regulated in tumors achieving partial response to thalidomide treatment (cases #2, #3, and #7); while remained largely unchanged in thalidomide non-responsive MALT lymphomas (cases #4, #5, #8, and #9, Fig. 3). Down-regulations of nuclear NF-κB expression was also noted in the microenvironment of thalidomide complete responsive tumors (case #1 and #6, Fig. 3).

Changes of inflammatory cells and microvascular density

Only scant neutrophils were found in all baseline and post-thalidomide tissue samples. Whiles, the mean (±standard deviation) eosinophil counts in baseline and post-treatment tissue samples were 31.0 ± 16.7 and 16.0 ± 21.7/high-power field (HPF), respectively, in thalidomide responsive tumors, and 14.0 ± 8.6 and 18.4 ± 10.6/HPF, respectively, in non-responsive tumors (Fig. 4). The number of eosinophil in baseline tumor tissues of thalidomide responsive tumors was marginally more abundant than non-responsive tumors ($P = 0.077$, Student's t test). On the other hand, despite similar mean percentages of tumor infiltrating

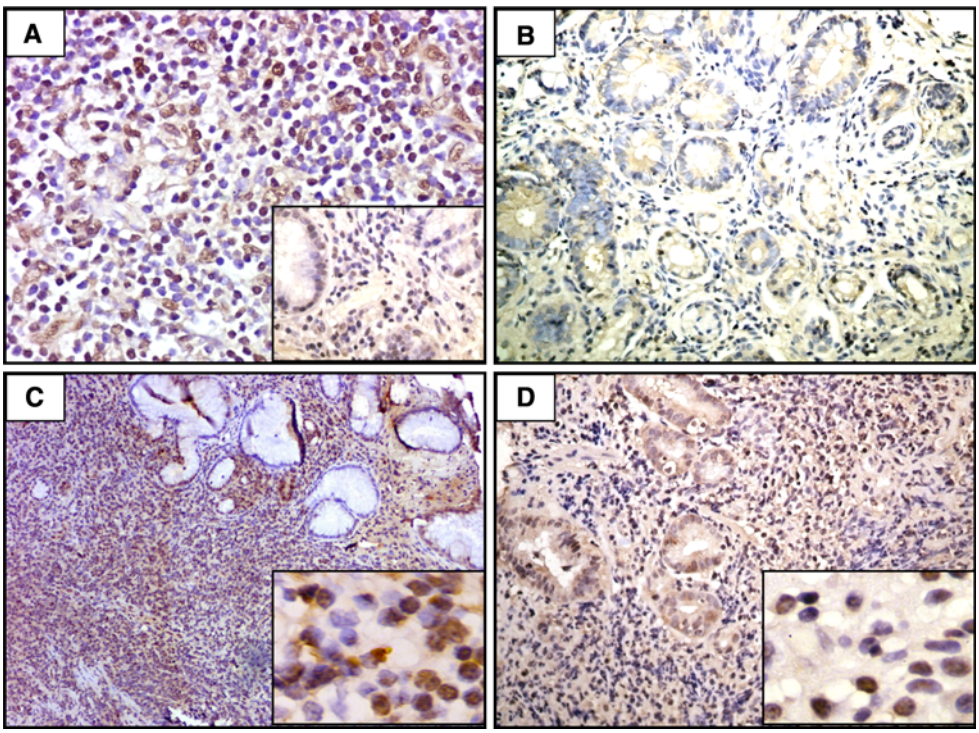
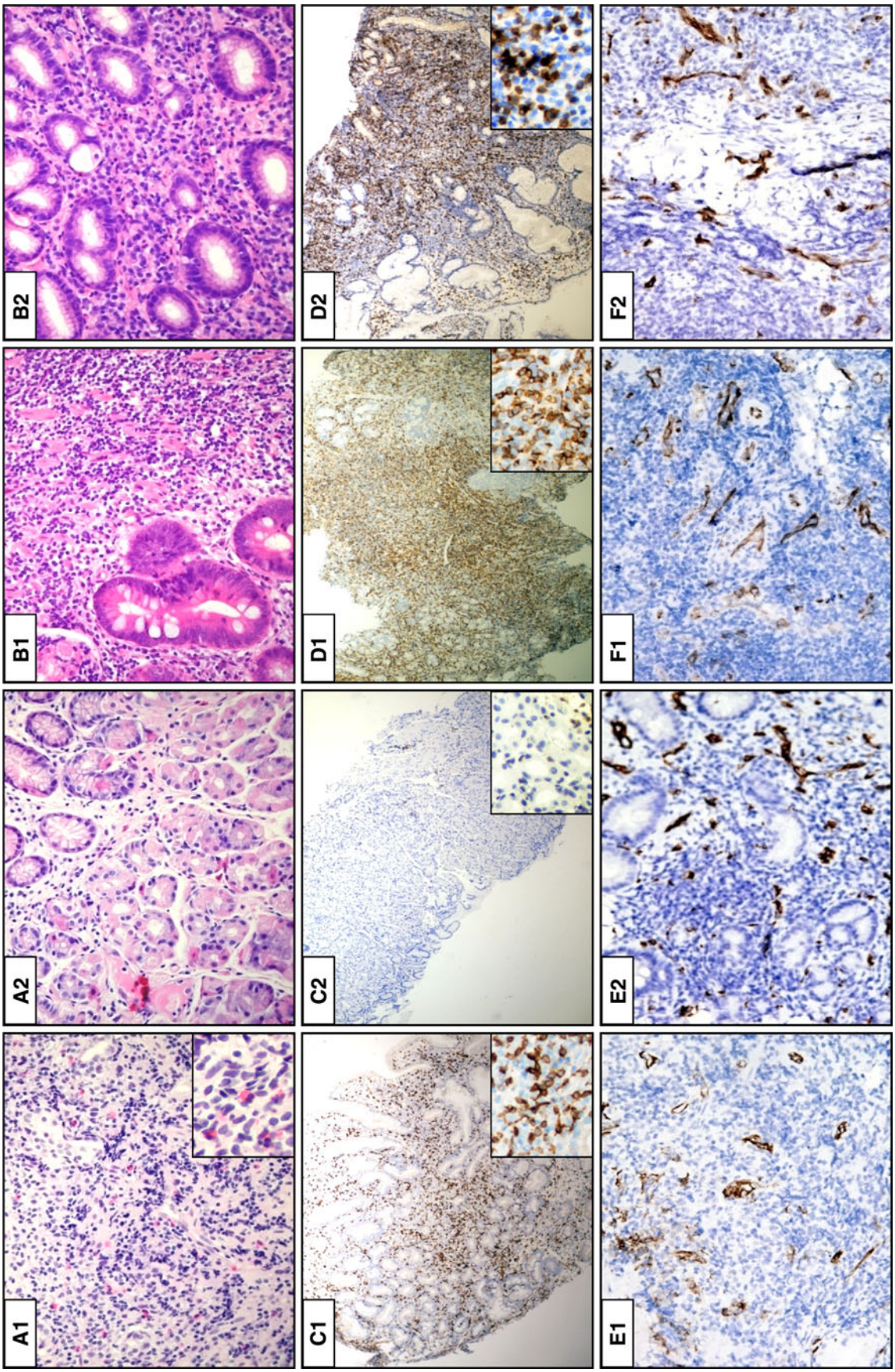


Fig. 3 The changes of NF-κB expression levels in tumor cells and tumor microenvironments before and after thalidomide treatment, **a** high baseline nuclear expression of NF-κB in tumor cells and microenvironment (right bottom inset, ×100) in case #1, **b** while the expression of NF-κB in microenvironment was no more detectable after achieving a complete response to thalidomide treatment (case #1); **c** high baseline nuclear expression level of NF-κB in tumor cells (right bottom inset, ×1,000) and microenvironment in case #9 (API2-MALT1, positive), **d** which remained unchanged after achieving a stable disease to thalidomide treatment (nuclear expression level of NF-κB in tumor cells, right bottom inset, ×1,000, case #9)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◀ **Fig. 4** The changes of eosinophils, CD3-positive T cell, and CD34-positive microvascularity in microenvironment before and after thalidomide treatment, **A1** abundant eosinophils in baseline tissue specimens in case #1 (right bottom inset, ×1,000), **A2** which was barely seen after achieving a complete response to thalidomide treatment (case #1); **B1** rare eosinophils in baseline tissue specimens in case #10, **B2** which remained unchanged after achieving a stable disease to thalidomide treatment (case #10); **C1** prominent tumor-infiltrating CD3-positive T cells in baseline tissue specimens in case #6 (right bottom inset, ×1,000), **C2** which showed significant decrease in number after achieving a complete response to thalidomide treatment (right bottom inset, ×1,000, case #6); **D1** prominent tumor-infiltrating CD3-positive T cells in baseline tissue specimens in case #4 (right bottom inset, ×1,000), **D2** which showed slight decrease in number after achieving a stable disease to thalidomide treatment (right bottom inset, ×1,000). There were no significant changes of microvascularies in the microenvironment before and after thalidomide treatment in thalidomide responsive case #2 (**E1** and **E2**), and thalidomide non-responsive case #9 (**F1** and **F2**)

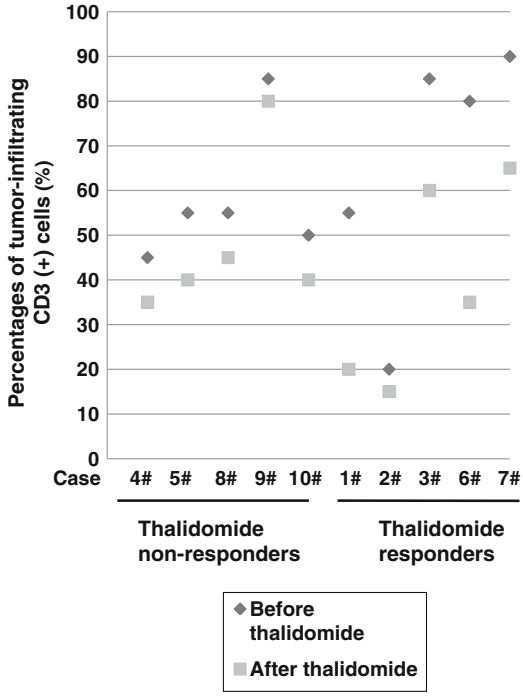

Fig. 5 Histograms showing the changes of mean percentages ± standard deviation of CD3-positive T cells in baseline and post-thalidomide tissue specimens of thalidomide non-responsive (case 4#, 5#, 8#, 9#, and 10#) and responsive tumors (case 1#, 2#, 3#, 6#, and 7#)

CD3-positive T cell in baseline tumor tissue samples, [66.0 ± 29.0%/lower-power field (LPF) of thalidomide responsive tumors vs. 58.0 ± 15.7%/LPF of thalidomide non-responsive tumors, $P = 0.602$], thalidomide treatment resulted in a more drastic decrease in CD3-positive cells composition in post-treatment tumor tissues of thalidomide responsive tumors than non-responsive tumors with an absolute reduction of 29.0 ± 18.2%/LPF versus 10.0 ± 3.5%/LPF ($P = 0.051$) (Figs. 4, 5). However, there was no significant difference of CD34-positive MVD between thalidomide responsive and non-responsive tumors in either baseline (27.8 ± 5.4/0.375 mm^2 vs. 22.5 ± 4.0/0.375 mm^2, $P = 0.172$) or post-treatment tumor tissue samples (23.3 ± 5.9/0.375 mm^2 vs. 26.0 ± 8.7/0.375 mm^2, $P = 0.619$), as shown in Fig. 4.

Discussion

In this study, we showed that low-dose (100–200 mg/day) thalidomide could achieve a 50% objective response rate in 10 patients with *H. pylori*-independent, standard therapy-failure gastric MALT lymphoma. Recently, Smith et al. and Pro et al. showed that thalidomide has only limited single-agent activity against heavily pretreated recurrent or refractory lymphoma, with objective response rates of 12.5 and 5.3%, respectively [25, 26]. However, one of the two patients with MALT lymphoma in these two studies achieved a durable complete remission after thalidomide therapy. In addition, Kees et al. had also described one patient with low-dose thalidomide/dexamethasone responsive extra-gastric MALT lymphoma [27]. These observations suggest that, in contrast to other categories of indolent lymphoma (with the exception of mantle cell lymphoma), thalidomide can be an effective salvage treatment for *H. pylori*-independent MALT lymphoma. On the other hand, no objective response was observed among the eight patients with refractory MALT lymphoma in the series of Troch et al. and the reasons for the discrepancy between these studies remains obscure [28].

In current study, we surprisingly noted that the presence of API2-MALT1 fusion transcript is associated with thalidomide resistance in *H. pylori*-independent gastric MALT lymphomas. None of four API2-MALT1 transcript-positive tumors responded to thalidomide, while 83% of API2-MALT1 transcript-negative tumors responded, $P = 0.048$ (Fisher's exact test). Of those responsive tumors, thalidomide treatment resulted in a decrease in nuclear NF-κB expression levels in residual neoplastic cells and in microenvironments of partial response tumors (cases #2, #3, and #7), and in microenvironments of complete response tumors (cases #1 and #6). The findings suggest that inhibiting NF-κB-related signaling pathways within tumor cells per se or microenvironment, or in combination may attribute to the anti-tumor activity of thalidomide against *H. pylori*-independent, API2-MALT1 transcript-negative gastric MALT lymphoma, as indicated in our previous work [10, 11].

In contrast, all four tumors with API2-MALT1 fusion transcript had persistent NF-κB nuclear expression after thalidomide treatment (example of case #8, Fig. 3) and were refractory to the treatment. It has been shown that the

presence of the API2-MALT1 fusion transcript can enhance NF-κB activation, which may in turn trans-activate both the API2 and the API2-MALT1 genes to form a positive feedback loop pathway to constitutively activate NF-κB so as to confer survival advantage for t(11;18)(q21;q21) translocation-positive gastric MALT lymphomas [1, 3, 7, 29–31]. Hence, we speculate that autocrine API2-MALT1/NF-κB signaling pathways may be less susceptible to thalidomide inhibition than the "classic" and "alternative" NF-κB signaling pathways in API2-MALT1 negative tumors to account for the difference in response to thalidomide between these two groups of tumors.

In addition, thalidomide treatment resulted in decreases in infiltrating eosinophils and CD3-positive T cells within the microenvironment of most responsive tumors, but microvascular density remained largely unchanged. These observations suggest the anti-MALT lymphoma activity of thalidomide is mainly through its immuno-modulating and anti-inflammatory activity, but not anti-angiogenic property.

In conclusion, our study showed that thalidomide is an effective salvage treatment for *H. pylori*-independent, t(11;18)(q21;q21)-negative gastric MALT lymphoma through modulation of tumor microenvironment-related immune reaction and elimination of inflammation-related signals such as TNF-α-related autocrine and/or paracrine pathways, which sustain growth of MALT lymphoma cells. On the other hand, the t(11;18)(q21;q21)-positive tumors were resistant to thalidomide therapy, likely through the activity of autocrine API2-MALT1/NF-κB signaling pathways. A confirmative prospective study is warranted.

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Conflict of interest The authors declare no competing financial interests.

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