Conjunctival lymphomas in Japanese monozygotic twins: A case report

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Abstract. An individual with a twin who has developed leukemia or non-Hodgkin lymphoma (NHL) has an increased risk of developing the same disease, particularly with monozygotic twins. The few reported pairs of twins who developed NHL had similar primary sites and pathological subtypes. Here, we present the first reported cases of primary conjunctival NHL in both female monozygotic twins. Twin 1 was diagnosed with an extranodal marginal zone lymphoma (EMZL; Ann Arbor stage I_E) in the right conjunctiva at 25 years old and a subsequent tumor in the left conjunctiva at 39 years, and was also histopathologically diagnosed as EMZL. No infiltration of other organs was detected and both lesions were surgically excised. At the age of 40 years, Twin 2 was diagnosed with an EMZL (Ann Arbor stage I_E) in the right conjunctiva without infiltration of other organs and was treated with external beam radiation therapy rather than surgery. Complete remission was achieved in both twins; neither developed conjunctival recurrences. This study highlights the importance of examining the other, apparently healthy twin when one twin develops conjunctival lymphoma.

Introduction

Siblings, particularly twins, are at similar risk of developing leukemia or non-Hodgkin lymphoma (NHL) (1,2), presumably due to similarities in both genetic and environmental factors. In a cohort of child cancer survivors including 211 twin pairs (1), the standardized incidence ratio (SIR) for all malignancies in all twins was 8.2 (95% confidence interval [CI], 3.9-17.1), compared with an SIR of 1.9 (95% CI, 1.7-2.1) in non-twin siblings, with an even higher SIR in monozygotic twins of 23.3 (9% CI, 11.1-48.9). Notably, the SIR for NHL was particularly high in monozygotic twins, at 40.5 (95% CI, 5.7-287.5) (1). A few reported cases of NHL occurring in both members of a pair of twins have been pathologically classified as similar types. We herein present the first report of primary conjunctival NHL that developed metachronously in each of a pair of monozygotic twins. Complete remission (CR) was achieved with different therapeutic strategies in each twin.

Case report

Twin 1 (treated at another hospital). The present team discovered Twin 1's medical history while treating Twin 2. Twin 1's attending physician was subsequently interviewed and the relevant biopsy specimen slides were sent to our hospital and reviewed by the present team.

A tumor associated with papillary changes was detected in the right conjunctiva in a 25-year-old woman and diagnosed as an extranodal marginal zone lymphoma (EMZL) by examination of a biopsy specimen. No infiltration of any other organs was detected and the EMZL was staged as Ann Arbor stage I_E. The tumor was excised and the patient (Twin 1) was closely followed up. At the age of 39 years, an asymptomatic conjunctival tumor was detected in the contralateral upper and lower conjunctiva (Fig. 1) and monitored. It did not regress and was therefore completely excised. Histopathological examination revealed lympho-epithelial lesions with monotonous infiltration of small atypical lymphocytes extending into the epithelium. Reactive follicle formation at the center of the lesion was accompanied by follicular colonization. On immunostaining, the lesion was positive for cluster of differentiation (CD) 20 and negative for CD10. On the basis of these findings, an EMZL was again

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Abbreviations: EBRT, external beam radiation therapy; EMZL, extranodal marginal zone lymphoma; FDG-PET/CT, fluorodeoxyglucose-positron emission tomography/computed tomography; NHL, non-Hodgkin lymphoma

Key words: conjunctival lymphoma, monozygotic twins, EMZL

diagnosed (Fig. 2). Detailed protocols of the experimental procedures for Twin 1 are unavailable, but staining was performed and the magnifications are shown. No infiltration of any other organs was detected by either fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT) or bone marrow biopsy and the EMZL was staged as Ann Arbor stage I_E. At the time of writing, Twin 1 had been closely followed up for 1.5 years since the most recent surgery, with no recurrence.

Twin 2 (treated at our hospital). Twin 1's monozygotic twin sister, Twin 2, presented with the sensation of a foreign body in the right lower conjunctiva at age 38 years. Three months later, at age 39 years, a tumor with papillary changes was detected in the right lower conjunctiva. Although examination of a biopsy of the same lesion revealed lymphocytic infiltration, no evidence of lymphoma was detected. Twin 2 was closely followed up and a second biopsy of the tumor in the right lower conjunctiva taken at the age of 40 years because the lesion had grown (Fig. 3). Histopathological examination revealed massive infiltration of small to medium-sized lymphocytes with atypical centrocytes under the epithelium. The lesion contained closely packed follicles and no tangible body macrophages were identified in the germinal centers of the reactive follicles. The follicular cells were positive for CD20 and almost negative for CD10. A pattern of CD21 staining was detected in the follicular dendritic cells, which had created well-formed meshworks. Bcl-2 protein was expressed not in the germinal center but in the peripheral zone of follicles. Bcl-6-positive cells in the interfollicular areas were Bcl-2-negative and these Bcl-6-positive cells were the remaining reactive follicular center cells. Ki-67-positive cells had lost polarity and there were a few large centroblastic cells. Thus Twin 2 was diagnosed as EMZL with intense follicular colonization (Fig. 4). No infiltration of any other organs was detected by FDG-PET/CT and the EMZL was staged as Ann Arbor stage I_E. Because this tumor widely involved the conjunctiva and it was believed that the completely excision was difficult, external beam radiation therapy (EBRT) was administered. Because the lesion involved the conjunctival surface in a way that was undetectable by magnetic resonance imaging, the entire conjunctiva was irradiated with a 5-MeV electron beam. A lead shield was placed on the cornea to prevent development of a radiation-induced cataract. CR was achieved by irradiation at a dose of 2 Gy/fraction to a total dose of 30 Gy. There were no adverse effects of radiation therapy. Twin 2 has been closely followed up for 6 months after this therapy to date, with no recurrence.

Hematoxylin and eosin staining (Twin 2). Sections (4 μm) were cut from each paraffin-embedded, formalin-fixed (FFPE) tissue blocks and stained with Mayer's hematoxylin (Sakura Finetek Japan Co., Ltd., Tokyo, Japan) and eosin-floxine (Sakura Finetek Japan Co., Ltd.) using by Tissue-Tek ® prisma (Sakura Finetek Japan Co., Ltd.). Mayer's hematoxylin was reacted for 3 min at room temperature, and eosin-floxine was reacted for 3 min at room temperature.

Immunohistochemistry (Twin 2). Sections (4 μm) were deparaffinized and treated with Envision Flex High pH

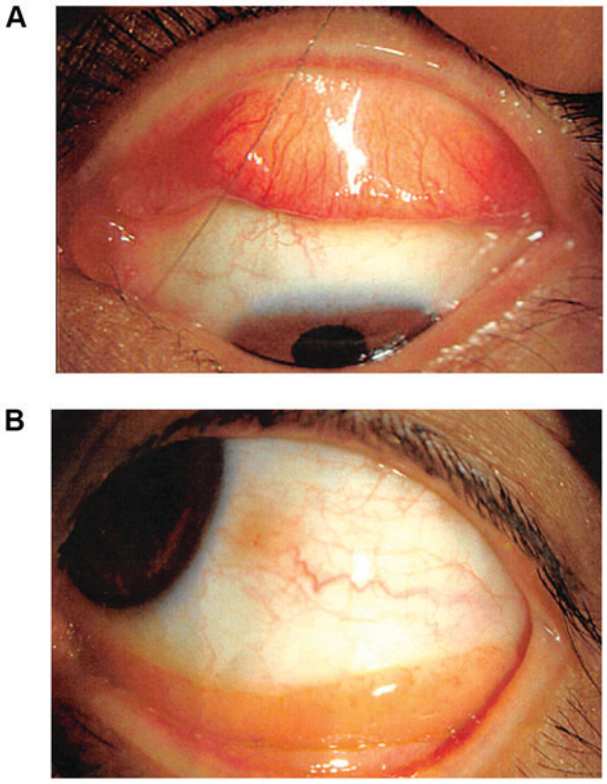

Figure 1. Conjunctival tumors were detected in the contralateral upper and lower conjunctiva. Photographs demonstrating the conjunctival tumors in the upper (A) and lower conjunctiva (B). Detailed magnifications of these photographs are unavailable as they were taken at another hospital.

visualisation system (Dako; Agilent Technologies Inc., Santa Clara, CA, USA), as antigen retrieval, for 20 min at 97˚C in a microwave and blocked using Peroxidase-Blocking Solution (Dako; Agilent Technologies, Inc.) at room temperature for 5 min. The immunohistochemical stainings were performed using by Autostainer Link 48 (Dako; Agilent Technologies, Inc.). Primary antibodies were used in the present study as follows: B-cell lymphoma 2 (Bcl2; clone SC-509; host, mouse; Santa Cruz Biotechnology, Inc., Dallas, TX, USA, cat no. M0887; 1:50), Bcl6 (clone, PG-B6p; host, mouse; Dako; Agilent Technologies, Inc.; cat no. IR625), CD10 (clone, 56C6; host, mouse; Novocastra, Leica Microsystems GmbH, Wetzlar, Germany.; cat no. NCL-CD10-270; 1:10), CD20 (clone, L26; host, mouse; Dako; Agilent Technologies, Inc.; cat no. IR604; 1:1,600), CD21 (clone, 1F8; host, mouse; Dako; Agilent Technologies, Inc.; cat no. IR608). Counterstaining was performed with hematoxylin. All of the assays were validated using proper positive controls tonsil FFPE tissue sections. Results were evaluated using a light microscope (BX-41, Olympus Co., Tokyo, Japan). The positive cut-off for all antibodies was considered to be 30% (3).

Detection of immunoglobulin gene rearrangements by BIOMED-2 study protocols. To analyze immunoglobulin gene clonal rearrangements by multiplex PCR, we used the BIOMED-2 primer system (4). In the BIOMED-2 guidelines, three sets of VH FR regions primers (FR1:6 primers, FR2:7 primers, and FR3: 7 primers) and a JH primer were designed. Furthermore, immunoglobulin kappa chain (IGK)

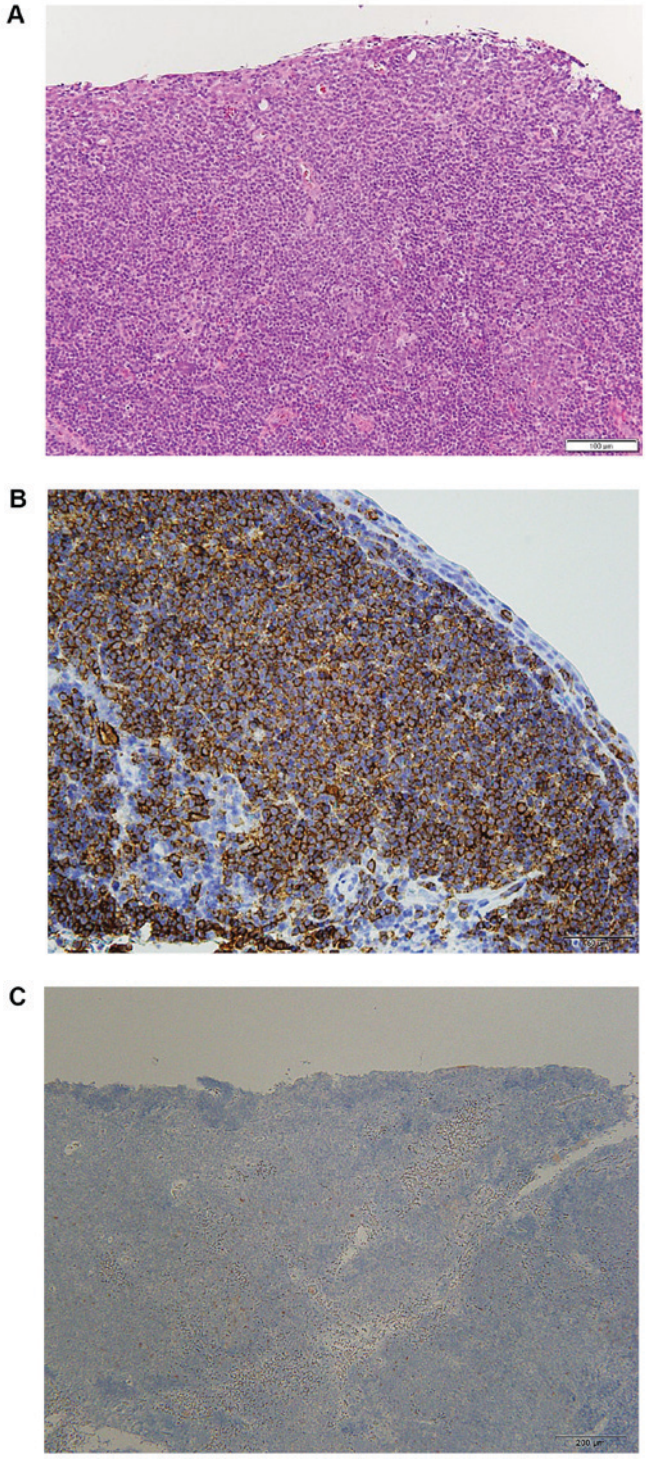

Figure 2. Histological and immunohistochemical findings in Twin 1's conjunctival tumor. (A) Lympho-epithelial lesion with monotonous infiltration of atypical lymphocytes extended into the epithelium and reactive follicle formation at the center of the lesion was accompanied by follicular colonization (magnification, x200; hematoxylin and eosin). (B) Immunohistochemical staining showing the lesion to be diffusely positive for CD20 (magnification, x400). (C) No CD10-positive cells were identified in the interfollicular area (magnification, x100).

VH primers (FR: 6 primers) and two sets of JH primers (JH1: 2 primers and JH2: 1 primer), and immunoglobulin lambda chain (IGL) VH primer and JH primer were prepared as previously reported by Lu *et al* (5). RNase P was used as the internal control. The PCR products were analyzed by agarose

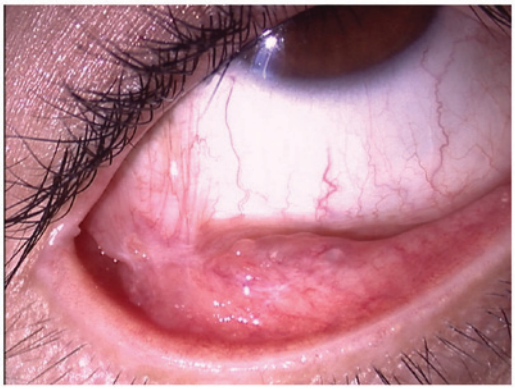

Figure 3. Photograph demonstrating the conjunctival tumor in the lower conjunctiva. Magnification, x10.

gel electrophoreses. Clonal immunoglobulin gene rearrangements were found by multiplex PCR, but the patterns of these rearrangement were different between both Twin 1 and Twin 2. In Twin 1, clonal rearrangement was detected by IGH FR2 primer set, and by IGH FR1 primer set in Twin 2. In both Twin 1 and Twin 2, IGK (kappa chain) were detected but IGL (lambda chain) were absent. Multiplex PCR analysis showed that immunoglobulin kappa light chain was dominant in both twins (data not shown).

Fluorescence in situ hybridization for immunoglobulin heavy chain (IGH)-mucosa associated lymphoid tissue lymphoma translocation gene 1 (MALT1) rearrangement detection. Four-micrometer sections were cut and deparaffinized with xylene. Glass slides were heated at 70˚C for 10 min. After the hydrophilic procedure and washing, the samples were placed in citric buffer at 98˚C for 15 min. After washing, proteinaseK solution was added to the samples and incubated at room temperature for 15 min. Next, Cytocell aquarius t(14;18)(32.33:21.31-21.32)/IGH-MALT1 dual fusion probe (Cytocell Ltd., Cambridge, UK) was added to the individual samples and the samples were covered with coverslips. After sealing the coverslips, the samples were denatured at 75˚C for 10 min and the slides were transferred to a hybridization oven overnight at 37˚C. Further processing included washing and counterstaining with DAPI. Signals were detected using an Axio Imager Z2 with a fluorescent microscope (Carl Zeiss Microscopy, Jena, Germany) with appropriate filters (Chroma Technology Corporation, Bellows Falls, VT, USA). The images were analyzed with the ZEN2 Pro software (Carl Zeiss Microscopy). These results showed the not rearranged IGH-MALT1 signals in both twins' samples (data not shown).

Species-specific real-time PCR for the diagnosis of Chlamydia psittaci (C. psittaci) infection. DNA samples were extract from formalin fixed and paraffin embedded (FFPE) sections using by the commercial kit (GeneRead DNA FFPE kit, Qiagen GmbH, Hilden, Germany). The first PCR reaction was carried out with each DNA by using the AmpliTaq Gold® 360 Master Mix (Thermo Fisher Scientific, Inc., Waltham, MA, USA) and the species-specific primers that have been reported by Opota *et al* (6). Samples were incubated at 95˚C for 10 min before being subjected to 40 cycles of denaturation at 95˚C for

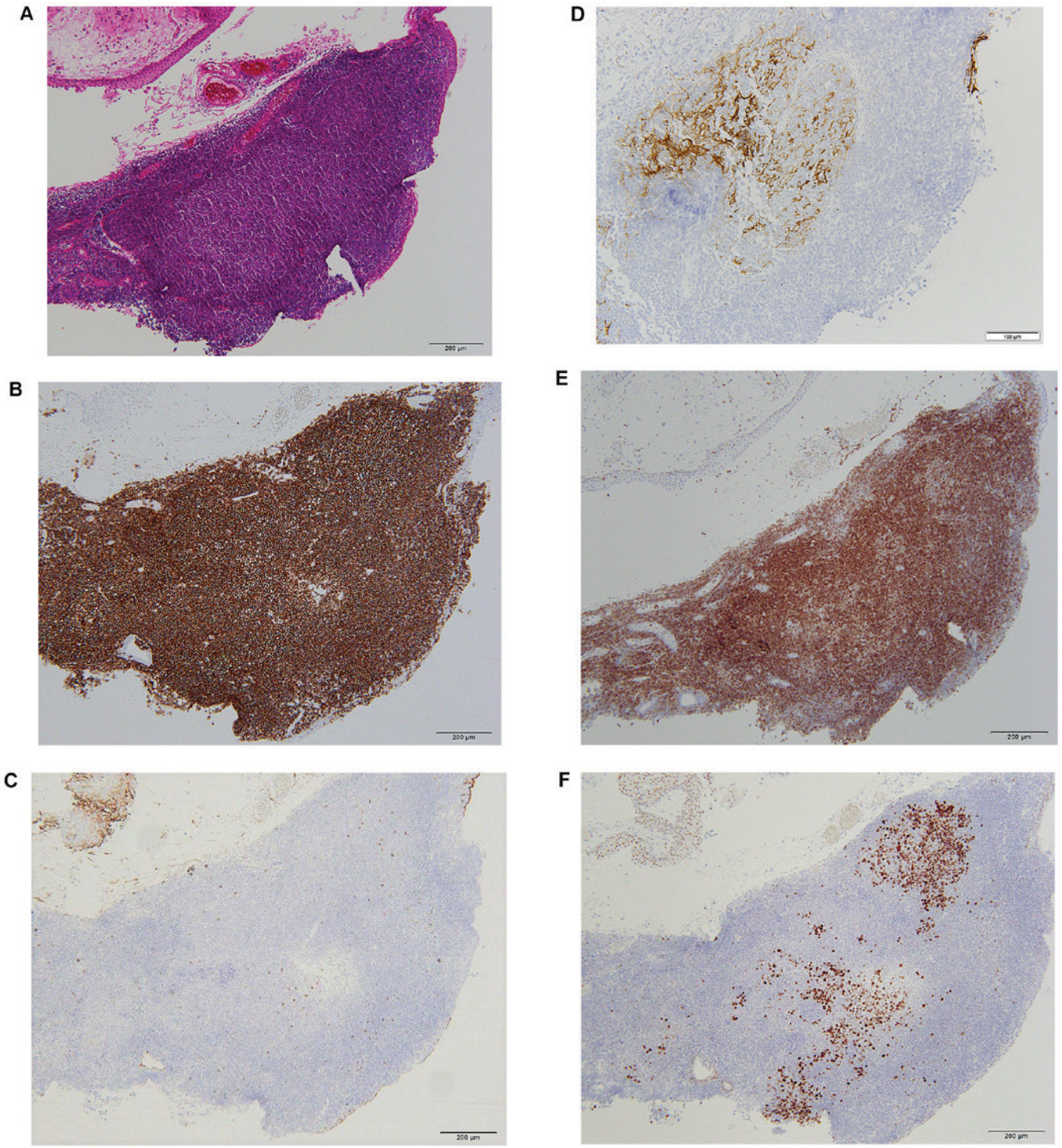

Figure 4. Histological and immunohistochemical findings in Twin 2's conjunctival tumor. (A) Lymphocytes with atypical centrocytes under the epithelium formed large follicles with intense follicular colonization (magnification, x100; hematoxylin and eosin). (B) Immunohistochemical staining showing that these follicular cells are positive for CD20 (magnification, x100) and (C) almost negative for CD10 (magnification, x100). (D) CD21 staining is apparent in follicular dendritic cells, which have created well-formed meshworks (magnification, x200). (E) Bcl-2 protein cells is expressed in the peripheral zone of follicles (magnification, x100). (F) Bcl-6-positive cells is expressed in the interfollicular area (magnification, x100).

30 sec, annealing at 60˚C for 1 min, and polymerization at 72˚C for 1 min. The first reaction was performed on a conventional PCR machine (PC808, ASTEC Co. Ltd., Fukuoka, Japan). Two microliters of each resulting product were used as the template in the second semi-nested (snq) PCR (7,8) amplification performed by QuantStudio 3 (Thermo Fisher Scientific, Inc.) with the species-specific primers, as same as the first PCR reaction, and TaqMan®probes that have been reported by Opota *et al* (6). TaqMan Copy Number Reference Assay, *RNase P*, Human (Thermo Fisher Scientific, Inc.) were used as an internal control gene. Although internal control gene *RNase P* was detected from both Twin 1 and Twin 2 sample DNA, neither *C. psittaci* nor *C. abortus* were detected from both twins (data not shown).

Table I. Overview of reported twin pairs with non-Hodgkin lymphoma.

				Twin 1		Twin 2		
Author, year	Pair	Twin type	Sex	Histology, invaded organ	Age, years	Histology, invaded organ	Age, years	(Refs.)
Granet, 1949	1	MZ	M/M	ML, rectum	31	ML, rectum	38	(9)
Schneider *et al*, 1995	2	MZ	F/F	T cell lymphoma, skin	46	T celllymphoma, skin	47	(10)
Jensen *et al*, 1997	3	MZ	F/F	EBV positive NHL, CNS	18	EBV positive NHL, CNS	19	(11)
Salawu *et al*, 1997	4	MZ	M/M	Burkitt's lymphoma, nodal	8	Burkitt's lymphoma, nodal	11	(12)
Marco *et al*, 1999	5	MZ	M/M	Follicular lymphoma, nodal	48	Follicular lymphoma, nodal	48	(13)
Chakravarti *et al*, 2005	6	DZ	M/F	Follicular lymphoma, nodal	52	Follicular lymphoma, salivary gland	53	(14)
Dickinson *et al*, 2011	7	MZ	M/M	Marginal zone lymphoma, skin	45	Marginal zone lymphoma, skin	45	(15)
Bahig *et al*, 2016	8	MZ	F/F	Marginal zone lymphoma, skin	18	Marginal zone lymphoma, skin	25	(16)
	The present case	MZ	F/F	Marginal zone lymphoma, conjunctiva	25 and 39	Marginal zone lymphoma, conjunctiva	40	

MZ, monozygotic; DZ, dizygotic; ML, malignant lymphoma not otherwise specified; EBV, Epstein-Barr virus; NHL, non-Hodgkin lymphoma not otherwise specified; CNS, central nervous system.

Discussion

When one member of a twin pair develops leukemia or NHL, the other member is at increased risk of developing the same disease. A cohort study on familial risk of NHL showed that the SIR for lifetime cumulative risk of NHL in siblings of an individual with NHL is 1.6 (95% CI, 1.2-1.9), compared with a cumulative lifetime risk for twins, depending on sex and age at diagnosis, of 3.1-12.9% (2). Possible reasons for both members of a pair of twins developing NHL include genetic factors, such as chromosomal translocation, and exposure to similar environmental factors as a result of living in the same region. Only eight instances of both members of a pair of twins developing NHL have been reported (Table I) (9-16). In all these cases, both twins had similar primary sites, the commonest being the skin, which was affected in three pairs. Moreover, both members of each of the eight twin pairs had similar pathological subtypes. No cases of NHL of the conjunctiva in twins have been reported to date. The current case report is the first to document the development of conjunctival NHL in monozygotic twins.

NHL is reportedly associated with several chromosomal translocations and genetic factors may be considered to be responsible in our pair of twins. In recent years, to diagnose B-cell lymphoma, the immunoglobulin gene rearrangement detection system is used as a valuable tool (5). Our both twins have clonal B-cell immunoglobulin gene rearrangements, but the patterns of these rearrangements were different between Twin 1 and Twin 2. Recently, t(14;18)(q32;q21) involving the IgH/MALT1 has been reported in ocular adnexal mucosa-associated lymphoid tissue (MALT) lymphoma (17). However, our both twins were negative for t(14;18)(q32;q21).

Studies of monozygotic twins, who share a common genome, provide an effective way of assessing the potential contribution of environmental factors to NHL development. According to a questionnaire survey on medical history (e.g., infections and atopic disease) and microbial exposure history (e.g., sucking on a pacifier) in 162 twin pairs with discordant development of NHL, the risk of NHL was higher in the twin who had been more frequently exposed to microbes than their co-twin (18). Conjunctival lymphoma is believed to be caused by prolonged antigen stimulation resulting from chronic conjunctival infection with *Chlamydia psittaci* and other organisms, causing loss of B-lymphocyte control and 80% of ocular adnexal lymphoma samples carried *C. psittaci* DNA (19). Therefore to detect *C. psittaci* infection, we performed species-specific real-time PCR by using the primers that have been reported by Opota *et al* recently (6). However, our both twins were negative for *C. psittaci* in real-time PCR. *Helicobacter pylori* is associated with gastric MALT lymphoma but has not been identified in any reported cases of conjunctival MALT lymphoma (20). Because the twins in this case report lived together until Twin 1 developed her first conjunctival lymphoma at age 25 years, Twin 2 might have the another chronic infection at living alone. Autoimmune disorders such as Sjögren syndrome are also reportedly associated with conjunctival lymphoma; however, our twins had no history of such diseases. The commonest

subtype of conjunctival lymphoma is EMZL, accounting for 81% of all cases, whereas the second most common is follicular lymphoma (FL), accounting for 8% (21). The incidence of FL is lower in Asian countries, including Japan, than in the West, and only four cases of conjunctival FL in Japanese individuals have been reported to date (22-25). In the current twins, both NHL in the conjunctiva was EMZL.

EBRT is a highly effective and commonly administered therapeutic strategy for conjunctival lymphoma; nonetheless, complete surgical excision followed by monitoring is also sometimes performed. However, lymphoma cells may infiltrate the surrounding tissues at a microscopic level, resulting in a high recurrence rate in the absence of additional treatment, approximately one in three patients reportedly developing progression or recurrence during a 3-year follow-up (21,26). The total radiation dose of 30 Gy is generally considered sufficient to successfully and safely control conjunctival EMZL (27,28). In the current Twin 1, NHL developed in the contralateral conjunctiva 13.5 years after complete excision of the first NHL deposit; however, no further recurrence has been identified in either conjunctiva in the 1.5 years since the second surgery. The current Twin 2 was treated with EBRT alone, receiving a total dose of 30 Gy, and has since shown no recurrence in either conjunctiva. Ocular adnexal EMZL may develop in the contralateral orbit, the reported incidence being 6.4% even after radiation therapy (28). However, the prognosis of ocular adnexal EMZL is favorable, with a 10-year overall survival rate of approximately 95.3% (28). CR was achieved in both twins in the current case report with different therapeutic strategies being used. Further follow-up of both twins is essential.

We here provide the first reported cases of primary conjunctival NHL occurring metachronously in the conjunctiva of each of a pair of monozygotic twins. When NHL occurs in one of a twin pair, the other twin is at increased risk of developing NHL. When conjunctival lymphoma, which causes few symptoms, develops in a twin, it is therefore important to examine the other, apparently healthy twin.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

NI treated Twin 2 and analyzed the twins' data, as well as being a major contributor to writing the manuscript. SS biopsied the conjunctiva of Twin 2. HT examined Twin 2. HN and YN performed the histological examinations of the twins' samples. YC examined Twin 1. TM treated Twin 2. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The patients provided written informed consent.

Patient consent for publication

The patients provided written informed consent.

Competing interests

The authors declare that they have no competing interests.

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