ISSN 2218-4333 (online)

World Journal of *Clinical Oncology*

World J Clin Oncol 2019 November 24; 10(11): 358-381

Published by Baishideng Publishing Group Inc

WJCO

World Journal of Clinical Oncology

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World Journal of Clinical Oncology

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ABOUT COVER

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The *WJCO* is now abstracted and indexed in PubMed, PubMed Central, Emerging Sources Citation Index (Web of Science), China National Knowledge Infrastructure (CNKI), China Science and Technology Journal Database (CSTJ), and Superstar Journals Database.

RESPONSIBLE EDITORS FOR THIS ISSUE

Responsible Electronic Editor: *Mei-Yi Liu*

Proofing Production Department Director: *Xiang Li*

NAME OF JOURNAL
World Journal of Clinical Oncology

ISSN
ISSN 2218-4333 (online)

LAUNCH DATE
November 10, 2010

FREQUENCY
Monthly

EDITORS-IN-CHIEF
Hiten Patel

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/2218-4333/editorialboard.htm

EDITORIAL OFFICE
Ruo-Yu Ma, Director

PUBLICATION DATE
November 24, 2019

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World J Clin Oncol 2019 November 24; 10(11): 358-368

DOI: 10.5306/wjco.v10.i11.358

ISSN 2218-4333 (online)

ORIGINAL ARTICLE

Observational Study

Germline mutations in Thai patients with nonmucinous epithelial ovarian cancer

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Author contributions: Manchana T designed the research study, collected and analyzed the data and wrote the paper; Phowthongkum P provided genetic counseling, interpreted the genetic database and wrote the paper; Teerapakpinyo C performed germline mutation analysis and interpreted the genetic database.

Institutional review board statement: Institutional Review Board, Faculty of Medicine, Chulalongkorn University.

Informed consent statement: All study participants provided informed written consent prior to study enrollment.

Conflict-of-interest statement: All the authors have no conflict of interest.

STROBE statement: The authors have read the STROBE Statement-checklist of items, and the manuscript was prepared and revised according to the STROBE Statement-checklist of items.

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Abstract

BACKGROUND

Genetic testing is widely recommended for all epithelial ovarian cancer (EOC) patients. However, an increased probability of identifying germline mutations has been reported in selected patients with risk factors such as a family history or personal history of cancer and high-grade serous carcinoma (HGSC) subtype. HGSC has been reported to be the most common subtype of EOC worldwide (approximately 70%). However, this subtype is less prevalent in Thai patients (reported as only 20%). The difference in the distribution of various subtypes of EOC may reflect the incidence of germline mutations in Thai EOC patients.

AIM

To evaluate the frequencies of germline mutations in EOC patients and to compare the frequencies in those with and without clinical risk factors for hereditary ovarian cancer.

METHODS

This cross-sectional study included 112 nonmucinous EOC patients who underwent primary surgery at our tertiary care hospital. Clinical risk factors for hereditary ovarian cancer were defined as follows: Age below 40 years, a significant family history of cancer, synchronous ovarian and endometrial cancer, and HGSC. Comprehensive germline mutations were detected by next-generation sequencing.

Manuscript source: Invited manuscript

Received: March 2, 2019
Peer-review started: March 4, 2019
First decision: April 11, 2019
Revised: August 13, 2019
Accepted: November 4, 2019
Article in press: November 4, 2019
Published online: November 24, 2019

P-Reviewer: Zhang XQ
S-Editor: Yan JP
L-Editor: A
E-Editor: Liu MY

RESULTS

Of a total of 112 patients, 82 (73.2%) patients had ≥ 1 risk factor and 30 (26.8%) patients had no risk factors. Germline mutations were detected in 26 patients: 20 (17.8%) patients had *BRCA1/2* mutations, but 6 (5.4%) patients had mutations in other genes, including 1 in *MLH1*, 1 in *MSH2*, 1 in *RAD51C*, 2 in *ATM* and 1 in *CDH1*. Germline mutations were only detected in patients with risk factors (26 of 82, 31.7%), not in patients without risk factors ($P < 0.001$). A significant family history of cancer and HGSC were the only two significant risk factors associated with a higher proportion of germline mutations (56.3% *vs* 10% for those with and without a history of cancer, respectively, 40.8% *vs* 9.5% for those with and without HGSC). Germline *BRCA* mutations were detected in 38.8% of patients with HGSC but in only 1.6% of those with non-HGSC. An age below 40 years, personal history of breast cancer, and synchronous ovarian and endometrial cancer were not significant factors (14.3% *vs* 23.5%, 33.3% *vs* 21%, 22.2% *vs* 22.3%).

CONCLUSION

Approximately one-third of EOC patients with risk factors had germline mutations. Almost all germline *BRCA* mutations were found in patients with the HGSC subtype. Selected patients with HGSC and a family history of cancer should be initially considered for genetic analysis in Thailand.

Key words: *BRCA* mutation; Epithelial ovarian cancer; Germline mutation; Thai

Core tip: Germline mutations could not be detected in any epithelial ovarian cancer patients without risk factors such as age below 40 years, significant family or personal history of cancer, and high-grade serous subtype. Mutations were detected in approximately one-third of patients with these risk factors: 25% had *BRCA*1/2 mutations, 5% had mutations in other homologous recombination genes, and 2.5% had *MMR* mutations. Significantly more germline mutations were found in patients with a family history of cancer, especially ovarian cancer. Germline *BRCA* mutations were detected in 38.8% of patients with the high-grade serous subtype but in only 1.6% of those with a non-high-grade serous subtype. Selected patients with the high-grade serous subtype or a significant family history of cancer should initially be considered for genetic analysis in limited resource settings.

Citation: Manchana T, Phowthongkum P, Teerapakpinyo C. Germline mutations in Thai patients with nonmucinous epithelial ovarian cancer. *World J Clin Oncol* 2019; 10(11): 358-368
URL: https://www.wjgnet.com/2218-4333/full/v10/i11/358.htm
DOI: https://dx.doi.org/10.5306/wjco.v10.i11.358

INTRODUCTION

Although most epithelial ovarian cancers (EOCs) are sporadic, at least 10% of EOC patients have a genetic predisposition[1]. Risk assessment has been previously used to identify patients at risk for hereditary ovarian cancers and to offer genetic counseling and testing. These risk factors are as follows: Early age of onset, personal history of breast cancer, family history of breast, ovarian cancer, endometrial and colon cancer, and specific histologic subtype such as high-grade serous carcinoma (HGSC)[2]. HGSC has been reported to increase the risk of germline mutations. It has also been reported that approximately 20% of HGSCs harbor *BRCA* mutations[3]. Recently, the recommendation for genetic testing in EOC patients has changed. Various national professional societies such as the American College of Obstetricians and Gynecologists, the Society of Gynecologic Oncologists, and the National Comprehensive Cancer Network have recommended offering genetic counseling and testing for all women with EOC including fallopian tube cancers and primary peritoneal cancers irrespective of risk factors[4,5]. Firstly, some patients with germline

mutations will be missed if the testing is based on these current risk factors. Secondly, genetic results can predict treatment outcomes. Patients with *BRCA*-mutated EOC have increased platinum sensitivity response rates and significant improvement in survival rate compared with those with non-*BRCA*- mutated EOC[6]. Thirdly, novel targeted therapy with Poly (ADP-ribose) polymerase inhibitors has been reported to be a promising targeted therapy for *BRCA*-mutated cancers including homologous recombination (HR) gene-deficient ovarian cancers[7].

The frequency of germline mutations varies across different countries and ethnicities. The incidence of *BRCA* mutations has been reported to range from 5.8%-24.8%[8]. Our previous study reported that 11.4% of patients with nonmucinous EOC had *BRCA* mutations[9]. However, that study included a small number of patients, and the mutations were reported only in selected patients with risk factors for hereditary ovarian cancers such as a family history or personal history of cancer and HGSC. Therefore, the incidence of *BRCA* mutations in unselected EOC patients could be even lower than this number. The incidence of HGSC is a major predictive variable. Although it has been reported as the most common subtype worldwide at approximately 70%[3], only 20% of Thai patients have serous carcinoma[9,10]. The difference in the distribution of various subtypes of EOC between Thai patients and others worldwide may reflect the lower incidence of germline mutations in Thai EOC patients. The objective of this study is to evaluate the frequency of germline mutations in EOC patients and to compare the frequency in those with and without clinical risk factors for hereditary ovarian cancer.

MATERIALS AND METHODS

Ethic statements

This study was approved by the Institutional Review Board, Faculty of Medicine, Chulalongkorn University. This was a cross-sectional study conducted between November 2015 and February 2018.

Patients

Patients with EOC, fallopian tube or primary peritoneal cancer who underwent primary surgery and had a pathologically confirmed nonmucinous subtype were enrolled. Clinical risk factors for hereditary ovarian cancer are defined as follows: (1) Age at diagnosis below 40 years; (2) Significant family history (≥ 1 relative with ovarian cancer at any age, ≥ 1 relative with breast cancer or hereditary nonpolyposis colorectal cancer (HNPCC)-associated cancers such as colon cancer or endometrial cancer diagnosed before 50 years of age, ≥ 2 relatives with breast cancer or HNPCC-associated cancers diagnosed after 50 years of age; (3) Previous diagnosis of breast cancer; (4) Synchronous ovarian cancer and endometrial cancer; and (5) HGSC[9]. All patients who agreed to participate in this study received genetic counseling by a geneticist and provided informed consent.

Germline mutation analysis

Comprehensive germline mutation analysis was performed using peripheral blood DNA samples analyzed by a GeneRead DNAseq Mix-n-Match Panel v2 (27-gene panel including *APC, ATM, AXIN2, BARD1, BMPR1A, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, EPCAM, MLH1, MLH3, MRE11, MSH2, MSH6, MUTYH, NBN, PALB2, PMS2, PTEN, RAD50, RAD51C, RAD51D, SMAD4, STK11*, and *TP53*) (Qiagen) and next-generation sequencing (NGS) (The Illumina MiSeq System; Illumina, San Diego, CA, United States). DNA was extracted from the patients' peripheral blood using a QIAamp DNA Blood Mini Kit. DNA quality was assessed using GeneRead DNA QuantiMIZE Kits according to the manufacturer's instructions (Qiagen, Germany). DNA library preparation and NGS were performed as previously described[9]. Variant pathogenicity was classified based on the American College of Medical Genetics and Genomics and the American Society of Molecular Pathology standard and guidelines for the interpretation of sequence variants[11]. Variant classification was listed as "Pathogenic", "Likely pathogenic", "Variant of Uncertain Clinical Significance", "Likely benign" or "Benign" in decreasing order of clinical importance. The pathogenic and likely pathogenic variants found in this study were confirmed using bi-directional Sanger sequencing.

Statistical analysis

SPSS version 22 (SPSS Inc., Chicago, IL, United States) was used for the statistical analysis. Comparisons of the proportions of germline mutations between two groups were analyzed by Chi-square or Fisher's Exact test. *P* values less than 0.05 were considered statistically significant.

RESULTS

Patient characteristics

Of the 112 patients, 97 were diagnosed with EOC, 4 with fallopian tube cancer, 2 with primary peritoneal cancer, and 9 with synchronous endometrial and ovarian cancer. The mean age was 52.8 ± 11.0 years. Patient characteristics are shown in Table 1. Eighty-two patients (73.2%) had at least one clinical risk factor, and 27 patients (24.1%) had more than one risk factor. Of the 82 patients, EOC was diagnosed in 67 patients (81.7%), fallopian tube cancer in 4 patients (4.9%), primary peritoneal cancer in 2 patients (2.4%), and synchronous endometrial and ovarian cancer in 9 patients (11.0%). The histologic subtypes in these patients were HGSC in 49 patients (59.8%), low-grade serous carcinoma in 4 patients (4.9%), endometrioid carcinoma in 15 patients (18.3%), clear cell carcinoma in 12 patients (14.6%), mixed endometrioid and clear cell carcinoma in 1 patient (1.2%), and adenocarcinoma in 1 patient (1.2%). Thirty patients (26.8%) had no clinical risk factors of hereditary ovarian cancer, all of whom were diagnosed with EOC. The histologic subtypes in these patients were endometrioid carcinoma in 13 patients (43.3%), clear cell carcinoma in 12 patients (40%), mixed endometrioid and clear cell carcinoma in 3 patients (10%) and low-grade serous carcinoma in 2 patients (6.7%).

Germline mutation analysis

Germline mutations were detected in 26 patients (23.2%), whereas 20 patients (17.8%) had *BRCA*1 or *BRCA*2 mutations, and 6 patients (5.4%) had mutations in other genes (Table 2). Germline mutations could not be detected in any of the 30 patients without risk factors. In contrast, all mutations were detected in 26 of 82 patients with ≥ 1 risk factor (31.7%, $P < 0.001$). The frequency of germline mutations according to various risk factors is shown in Table 3. Significantly more germline mutations were observed in patients with a significant family history of cancer compared with patients without a significant family history (56.3% and 10% for with and without a family history of cancer, respectively, $P < 0.001$). Fourteen of 32 patients who had a family history of cancer had *BRCA* mutations (43.7%) and 3 patients (9.4%) had other gene mutations. In contrast, 6/80 (7.5%) patients without a family history of cancers had *BRCA* mutations and 2/80 (2.5%) had other gene mutations (1 *ATM* and 1 *CDH*1). Significantly higher frequencies of germline mutations were observed in patients with a family history of ovarian cancer (70% *vs* 17.6% for those with and without a family history of ovarian cancer, respectively, $P = 0.001$) and in patients with a family history of breast cancer (40.9% *vs* 17.8% for patients with and without a family history of breast cancer, respectively, $P = 0.04$). Patients with a family history of ovarian cancer had a higher frequency of *BRCA* mutations than those with a family history of breast cancer (60% *vs* 40.9%). If other genes were included, the frequency of germline mutations was 70% and 40.9%, in those with family history of ovarian and breast cancers, respectively. HGSC was also observed as another factor associated with a higher frequency of germline mutations (40.8% and 9.5%, $P < 0.001$). Nineteen patients with HGSC (38.8%) had *BRCA* mutations. Seven of 63 patients (11.1%) who had types other than HGSC had germline mutations; 1.6% had *BRCA* mutations and 7.9% had other gene mutations. A sub-analysis of 30 patients with HGSC without the other clinical risk factors revealed that the frequency of *BRCA* mutations was 16.7% (13.3% with *BRCA*1 mutations and 3.3% with *BRCA2* mutations). The frequency of germline mutations in patients with other risk factors such as age below 40 years, personal history of breast cancer, and synchronous cancer was not significantly different (14.3% *vs* 23.5%, 33.3% *vs* 21%, 22.2% *vs* 22.3%; $P > 0.05$)

Germline *BRCA* mutations were found in 20/82 (24.4%) patients with risk factors (14 *BRCA*1 mutations and 6 *BRCA*2 mutations). MMR mutations (*MLH1* and *MSH2*) were found in 2 (2.4%) patients who were diagnosed with synchronous endometrial and ovarian cancer. Other gene mutations such as *RAD51C*, *ATM* and *CDH1* were detected in 4 (4.9%) patients. The proportion of germline mutations is shown in Figure 1. Among 20 patients with *BRCA* mutations, 14 patients (70%) had a family history of breast and/or ovarian cancer, 19 patients (95%) had HGSC, 3 patients (15%) had a personal history of breast cancer, and 7 patients (35%) were older than 60 years at diagnosis.

DISCUSSION

At least 10% of EOCs are hereditary, and most germline mutations are associated with *BRCA*1 and *BRCA2*[1]. A 10%-15% frequency of germline *BRCA* mutations has been reported in unselected EOC patients[12-14]. However, mutations in MMR genes (*MLH1*,

Table 1 Patient characteristics of patients with and without clinical risk factors

Characteristics	Patients with risk factors (*n* = 82)	Patients without risk factor (*n* = 30)	*P* value
Mean age (yr)	51.8 ± 11.7	55.6 ± 8.3	0.06
Menopause, *n* (%)	39 (47.6)	17 (56.7)	0.52
Diagnosis, *n* (%)			
Epithelial ovarian cancer	67 (81.7)	30 (100)	0.10
Fallopian tube cancer	4 (4.9	0	
Peritoneal cancer	2 (2.4)	0	
Synchronous ovarian and endometrial cancer	9 (11.0)	0	
Histologic subtype, *n* (%)			
High-grade serous	49 (59.8)	0	< 0.001
Low-grade serous	4 (4.9)	2 (6.7)	
Endometrioid	15 (18.3)	13 (43.3)	
Clear cell	12 (14.6)	12 (40.0)	
Mixed endometrioid and clear cell	1 (1.2)	3 (10.0)	
Adenocarcinoma	1 (1.2)	0	
Stage, *n* (%)			
1	27 (32.9)	13 (43.3)	0.06
2	10 (12.2)	8 (26.7)	
3	38 (46.3)	9 (30.0)	
4	7 (8.5)	0	
Platinum sensitivity, *n* (%)	66 (80.5)	23 (76.7)	0.73
Germline mutation, *n* (%)	26 (31.7)	0	< 0.001

MSH2, *MSH6*, *PMS2*) associated with Lynch or HNPCC syndrome and other genes in HR pathways have been implicated in inherited susceptibility to ovarian cancer. Approximately a quarter of EOC patients carry germline mutations in HR genes, including *BRCA1*, *BRCA2*, and other HR genes such as *ATM*, *BARD1*, *BRIP1*, *CHEK1*, *CHEK2*, *FAM175A*, *MRE11A*, *NBN*, *PALB2*, *RAD51C*, and *RAD51D*. Moreover, about 6% of patients carry germline mutations in other HR genes[15,16]. The frequency of germline mutations in this study has been reported to be 31.7% in selected EOC patients with risk factors. Of these patients, 24.4% carried *BRCA1* or *BRCA*2 mutations and 7.3% had mutations in other genes. Other mutations found in this study include those in the *RAD51C*, *ATM*, *CDH1*, *MLH1*, and *MSH2* genes. The *RAD51C* and *ATM* genes are involved in DNA repair mechanisms similar to the *BRCA1* and *BRCA2* genes. These genes have been reported to increase the risk of developing breast and ovarian cancer[17]. Germline *CDH1* mutations are known to cause hereditary diffuse gastric cancer syndrome, which increases the lifetime risk of gastric, breast, and colon cancer. However, down-regulation of *CDH1* gene expression is involved in cancer invasion and metastasis in many cancers, including ovarian cancer[18]. Mutations in *MMR* genes are associated with Lynch syndrome, which increase the lifetime risk of colorectal, endometrial and ovarian cancer. The frequency of *MMR* mutations in this study was 1.8% (2/112 patients), which was slightly higher than that reported in previous studies (0.5%)[14]. A family history or personal history of Lynch syndrome-associated cancers was considered a risk factor in this study. Furthermore, our previous study reported that endometrioid carcinoma was the most common histological subtype among Thai EOC patients[10]. EOC patients with germline *MMR* mutations usually have the endometrioid subtype. These different subtypes might affect the different frequency of germline mutations in *MMR* genes in this study.

The selection criteria for germline testing in EOC patients included young age, a family or personal history of cancer, HGSC, and specific ethnicity. Using these criteria, 27.5% of patients with germline *BRCA* mutations might not have been selected for genetic testing[8]. Although germline *BRCA* mutations are rarely found in patients aged over 60 years, one-third to half of all *BRCA* mutations are found in this group of women[1]. Furthermore, a significant family history of cancer is absent in 27%-56% of patients with germline *BRCA* mutations[1]. Our study showed that 35% of patients with germline *BRCA* mutations were older than 60 years at diagnosis and 30% had no significant family history of cancer. In addition, each patient might have overlapping risk factors. Therefore, other risk factors such as HGSC or a personal history of cancer in these patients might explain the germline *BRCA* mutations.

Table 2 Details of epithelial ovarian cancer patients with germline mutations

Age (yr)	Gene	Mutation			Variant classification	Cancer	Family history of cancer	Synchronous cancers	Histology
		Nucleotide change	Protein change	Type					
63	*BRCA1*	c.1889delA	p.Asn630IlefsTer2	Frameshift	Pathogenic	Ovarian cancer IIIC	Ovarian cancer (sister)	-	High-grade serous
64	*BRCA1*	c.981_982delAT	p.Cys328Ter	Frameshift	Pathogenic	Ovarian cancer IIIB	Ovarian cancer (sister)	-	High-grade serous
56	*BRCA1*	c.5072C>A	p.Thr1691Lys	Missense	Likely pathogenic	Fallopian tube cancer IIA	-	-	High-grade serous
52	*BRCA1*	c.3748G>T	p.Glu1250Ter	Nonsense	Pathogenic	Peritoneal cancer IIIC	Breast cancer (mother) ovarian cancer (sister)	-	High-grade serous
46	*BRCA1*	c.2059C>T	p.Gln687Ter	Nonsense	Pathogenic	Ovarian cancer IIIC	Ovarian cancer (grandmother)	-	High-grade serous
72	*BRCA1*	c.3049G>T	p.Glu1017Ter	Nonsense	Pathogenic	Ovarian cancer IIIA	Breast cancer (2 sisters) endometrial cancer (mother)	-	High-grade serous
57	*BRCA1*	c.3770_3771delAG	p.Glu1257GlyfsTer9	Frameshift	Pathogenic	Ovarian cancer IIIC	Breast cancer (aunt)	-	High-grade serous
51	*BRCA1*	c.1426delC	p.His476MetfsTer2	Frameshift	Pathogenic	Ovarian cancer IVB	Breast cancer (niece)	-	High-grade serous
35	*BRCA1*	c.3020C>A	p.Ser1007Ter	Nonsense	Pathogenic	Ovarian cancer IIIC	Breast cancer (mother)	-	High-grade serous
63	*BRCA1*	c.3181delA	p.Ile1061Ter	Frameshift	Pathogenic	Tubal cancer IVB	-	-	High-grade serous
69	*BRCA1*	c.1155G>A	p.Trp385Ter	Nonsense	Pathogenic	Tubal cancer IC	-	-	High-grade serous
45	*BRCA1*	c.3049G>T	p.Glu1017Ter	Nonsense	Pathogenic	Ovarian cancer IVB	-	-	High-grade serous
62	*BRCA1*	c.4327C>T	p.Arg1443	Frameshift	Pathogenic	Peritoneal cancer IIB	Breast cancer (daughter) Breast and ovarian cancer (sister) endometrial cancer (sister)	-	High-grade serous
59	*BRCA1*	c.981_982delAT	p.Cys328Ter	Frameshift	Pathogenic	Ovarian cancer IIIC	Breast cancer (sister)	-	High-grade serous
49	*BRCA2*	c.4126G > T	p.Gly1376Ter	Nonsense	Pathogenic	Ovarian cancer IIIC	Breast cancer (sister) Prostate cancer (uncle) Colon cancer (uncle)	-	High-grade serous
56	*BRCA2*	c.7558C > T	p.Arg2520Ter	Nonsense	Pathogenic	Ovarian cancer IIIC	-	-	High-grade serous
60	*BRCA2*	c.3109C > T	p.Gln1037Ter	Nonsense	Pathogenic	Ovarian cancer IVB	Breast cancer (2 sisters)	Breast cancer	High-grade serous
49	*BRCA2*	c.1367_1368delAG	p.Lys457GlufsTer4	Frameshift	Pathogenic	Ovarian cancer IIIC	Ovarian cancer (mother)	Breast cancer	High-grade serous
40	*BRCA2*	c.22_23delAG	p.Arg8AlafsTer4	Frameshift	Pathogenic	Ovarian cancer IIIC	Breast cancer (sister)	-	Clear cell carcinoma
63	*BRCA2*	c.1405_1406delGA	p.Asp469	Nonsense	Pathogenic	Ovarian cancer IIB	-	Breast cancer	High-grade serous

46	*MLH1*	c.109G > A	p.Glu37Lys	Nonsense	Likely pathogenic	Ovarian cancer IIC and endometrial cancer IAG1	Colon cancer (grandfather, father and uncle)	-	Well differentiated serous and well differentiated endometrioid
48	*MSH2*	c.1183C > T	p.Gln395Ter	Nonsense	Pathogenic	Ovarian cancer IA and endometrial cancer IAG1	Endometrial cancer (aunt)	Endometrial cancer	Endometrioid
48	*CDH1*	c.1118C > T	p.Pro373Leu	Missense	Likely pathogenic	Ovarian cancer IC and endometrial cancer IAG3	-	Endometrial cancer	Endometrioid with clear cell
54	*RAD51C*	c.905-2A > C	Not applicable	Splice site loss	Likely pathogenic	Ovarian cancer IIIC	Ovarian cancer (mother)	-	High-grade serous
67	*ATM*	c.1402_1403delAA	p.Lys468GlufsTer18	Frameshift	Likely pathogenic	Ovarian cancer IA	-	Breast cancer (Triple-negative)	Clear cell
52	*ATM*	c.8431_8432delAA	p.Lys2811ValfsTer3	Frameshift	Likely pathogenic	Ovarian cancer IIIC	Colon cancer (mother, aunt) liver cancer (aunt)	-	Clear cell

The frequency of germline *BRCA* mutations in EOC patients with a significant family history of breast/ovarian cancer was 43.7% in this study, which was comparable with that found in previous studies (33%-55%)[12,19-21]. A family history of ovarian cancer increases the chance of identifying germline *BRCA* mutations compared with a family history of breast cancer (60% *vs* 40.9%). This finding is consistent with previous studies in Korea and Australia, which reported incidences of *BRCA* mutations of 55%-63% and 15%-35% for a family history of ovarian and breast cancers, respectively[13,21].

Germline *BRCA* mutations are particularly frequent in HGSC and have been reported as 11%-23%[12-14]. Our study reported a higher frequency of 38.8%. As mentioned previously, it is likely that each patient has overlapping risk factors. The frequency of germline *BRCA* mutations was 16.7% in patients with HGSC without other risk factors. Most patients (95%) with germline *BRCA* mutations had HGSC, which is somewhat higher than the 73.2% reported in a previous study[8]. In contrast, only 1.6% of patients with non-HGSC had *BRCA* mutations, and 7.9% of these patients had germline mutations in other genes. This finding is in agreement with that of a previous study, which reported that germline *BRCA* mutations were detected in less than 10% of endometrioid carcinomas and had a very low frequency in clear cell carcinoma[1].

The incidence rates of EOC differ according to various geographic locations. Rates are highest in Western countries and lowest in Asian countries[22]. The age-standardized incidence rate in Thailand has been reported at approximately 6.2 per 100000 people in 2018[22]. Thus, the incidence of germline mutations in EOC may vary by ethnicity and country. Germline *BRCA* mutations were identified in 13% of Malaysian, 13% of Japanese and 17% of Taiwanese[23-25]. A higher frequency has been reported in 23% of Indian patients, and even higher frequencies have been reported in Korean and Chinese patients (up to 26% and 28.5%, respectively)[25-27]. Different proportions of histologic subtypes are also a major variable. HGSC is the most common subtype worldwide with an incidence rate of 70%[3], but it is much less prevalent in Thai patients (20%-22%). The endometrioid and clear cell carcinoma subtypes are observed more frequently (up to 60%)[9,10]. The reason for the high prevalence of endometrioid and clear cell carcinoma in Thai patients is unknown. Geographic differences may be a possible explanation, as clear cell carcinoma is more prevalent in Asia than in Western countries[27].

In this study, the frequency of germline mutations in patients with risk factors was 31.7% overall and 24.4% for *BRCA* mutations but was 0% in patients without risk factors. According to our previous study, 30% of EOC patients were classified as high-risk for hereditary ovarian cancer[9]. Most of our patients had non-HGSC and did not have other clinical risk factors. Therefore, the weighted estimated overall frequency of germline mutations in unselected patients should be only 9.5% overall and only 7.3% for *BRCA* mutations. This number is lower than reported in previous studies from Western countries and some countries in Asia. A much higher proportion of EOC patients who had no clinical risk factors, and HGSC, might be a plausible explanation

Table 3 Frequency of germline mutations according to various clinical risk factors

Risk factors	Number of patients	*BRCA1*, *n* (%)	*BRCA2*, *n* (%)	Other genes, *n* (%)
None	30	0	0	0
Family history of cancers (breast/ovary/endometrium/colon)	32	10 (31.2)	4 (12.5)	4 (12.5) (1*ATM*, 1*RAD51C*,1 *MLH1*, 1*MSH2*)
Family history of breast cancer	22	6 (27.3)	3 (13.6)	0
Family history of ovarian cancer	10	5 (50.0)	1 (10.0)	1 (10.0) (*RAD51C*)
Personal history of breast cancer	12	0	3 (25.0)	1 (8.3) (*ATM*)
Two primary ovarian and endometrial cancer	9	0	0	3 (33.3) (1 *MLH1*, 1*MSH2*, 1*CDH1*)
High-grade serous carcinoma	49	14 (28.6)	5 (10.4)	1 (2.1) (*RAD51C*)
Young age (< 40 yr)	14	1 (7.1)	1 (7.1)	0

for the lower incidence of germline *BRCA* mutations in this study. In general, if the estimated probability of harboring germline mutations is more than 10%, genetic testing is considered cost-effective[28,29]. Nonetheless, genetic testing is rather uncommon in many countries including Thailand because of cost considerations, reimbursement and availability. Since the estimated frequency of germline mutations in unselected patients is below 10%, genetic testing in all EOC patients may not be cost-effective.

The strength of this study was that reliable and comprehensive NGS techniques were used to analyze *BRCA* genes and other genes associated with HR pathways. The limitation of this study was that not all EOC patients during the study period were included and not all were offered genetic testing. Selection bias might affect the reversed proportion between patients with and without risk factors in this study (73% *vs* 27%). The overall frequency of germline mutations in this study was presumed and estimated based on the 30% of patients with risk factors. Moreover, *BRCA* dysfunction by epigenetic silencing was not analyzed. Further studies with larger numbers of patients and multicenter trials should be conducted to better represent the incidence of germline mutations in the Thai population.

In conclusion, approximately one-third of EOC patients with risk factors for hereditary ovarian cancer had germline mutations (24.4% had *BRCA* mutations and 7.3% had mutations in other genes). However, patients without risk factors did not have germline mutations. The weighted estimated overall frequency of germline mutations in unselected EOC patients was less than 10% and only 7.3% for *BRCA* mutations. Selected patients with the high-grade serous subtype or a significant family history of ovarian/breast cancers should be initially considered for further genetic analysis and intervention in countries with limited resources.

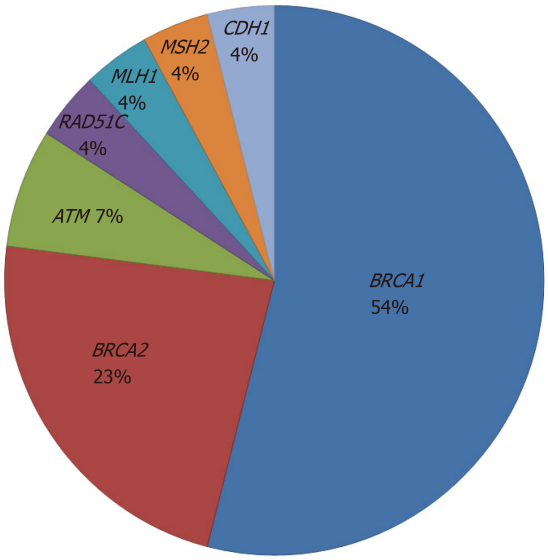

Figure 1 Proportion of germline mutations in patients with epithelial ovarian, fallopian tube, or peritoneal cancers.

ARTICLE HIGHLIGHTS

Research background

Genetic testing is widely recommended for all patients with epithelial ovarian cancer (EOC) including fallopian tube and primary peritoneal cancers. A 10%-15% incidence of germline *BRCA* mutations has been reported in unselected EOC patients. However, universal genetic testing in all patients may not be cost-effective if the estimated probability of harboring germline mutations is less than 10%. The incidence of germline mutations may vary across different countries and ethnicities. Different common histologic subtypes in various countries may be significant variables. The high-grade serous subtype is the most common subtype worldwide (approximately 70%), whereas it is less common in Thai EOC patients (rate of only 20%). Per this result, the incidence of germline mutations might be lower in unselected Thai EOC patients.

Research motivation

Different incidences of germline mutations in EOC patients among various countries may guide different recommendations for genetic testing. Universal genetic testing in all EOC patients may not be cost-effective in Thailand. The risk factors associated with the increased likelihood of having germline mutations should be evaluated.

Research objectives

The objective of this study was to evaluate the frequency of germline mutations in EOC patients and to compare the frequency in those with and without clinical risk factors for hereditary ovarian cancer.

Research methods

This cross-sectional study was conducted on 112 nonmucinous EOC patients including those with fallopian tube and primary peritoneal cancers who underwent primary surgery at our tertiary care hospital between November 2015 and February 2018. Patients were divided into two groups based on clinical risk factors for hereditary ovarian cancer as follows: Age below 40 years, significant family history of cancer, synchronous ovarian and endometrial cancer, and high-grade serous carcinoma (HGSC). All patients who agreed to participate in this study received genetic counseling by a geneticist and provided informed consent. Comprehensive germline mutations were detected using next-generation sequencing.

Research results

Germline mutations were detected in 26 of 112 patients (23.2%); 20 patients (17.8%) had *BRCA1* or *BRCA2* mutations, but 6 patients (5.4%) had mutations in other genes including 1 with an *MLH1*, 1 with an *MSH2*, 1 with a *RAD51C*, 2 with an *ATM* and 1 with a *CDH1* mutation. All mutations were detected in 26 of 82 patients with ≥ 1 risk factor (31.7%), but none were detected in the 30 patients without risk factors ($P < 0.001$). A significantly higher frequency of germline mutations was found in patients with a significant family history of cancer (56.3% and 10%, $P < 0.001$). Patients with a significant family history of ovarian cancer had a higher frequency of *BRCA* mutations than those with a family history of breast cancer (60% and 40.9%, respectively). HGSC was also associated with a higher frequency of germline mutations (40.8% and 9.5%, $P < 0.001$). Germline *BRCA* mutations were detected in 38.8% of patients with HGSC but in only 1.6% of those with non-HGSC. Other risk factors such as age below 40 years, personal history of breast cancer, and synchronous ovarian and endometrial cancer were not significantly different

in terms of germline mutations (14.3% *vs* 23.5%, 33.3% *vs* 21%, 22.2% *vs* 22.3%, $P > 0.05$).

Research conclusions

A significant family history of cancer and HGSC were the only two significant risk factors associated with a higher frequency of germline mutations. Germline *BRCA* mutations were detected in 38.8% of patients with HGSC but in only 1.6% of those with non-HGSC. According to the reverse proportion of histologic subtypes in Thai patients, the estimated overall frequency of germline mutations in unselected EOC patients should be only 9.5% overall and only 7.3% for *BRCA* mutations. These findings suggest the consideration of genetic testing in selected EOC patients in Thailand.

Research perspectives

Although universal genetic testing in all EOC patients is recommended by various national professional societies, it may not apply in every country. The narrow availability of genetic testing, the high cost when not reimbursed, and the limited number of geneticists are major obstacles in Thailand. Selected EOC patients should initially be considered for genetic analysis. As the number of patients in this study is still small and since the study was conducted in only one tertiary hospital, it may not fully represent the Thai population. Further prospective studies with multicenter trials should be conducted. The incidence of germline mutations should be studied in unselected EOC Thai patients to identify significant risk factors. Furthermore, *BRCA* genes should not be the only focus of germline mutation studies, but these studies should also be expanded to include other homologous recombination and MMR genes.

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World Journal of Clinical Oncology

Submit a Manuscript: https://www.f6publishing.com

World J Clin Oncol 2019 November 24; 10(11): 369-374

DOI: 10.5306/wjco.v10.i11.369

ISSN 2218-4333 (online)

CASE REPORT

Breathing adapted radiation therapy for leukemia relapse in the breast: A case report

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Informed consent statement: We obtained informed consent for

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Abstract

BACKGROUND

Infiltration of the breast by leukemic cells is uncommon but may manifest as an oncological emergency requiring prompt management. Extramedullary relapse of T-cell acute lymphoblastic leukemia (T-ALL) within the breast is exceedingly rare and there is paucity of data in the literature regarding this entity. No consensus exists on management of isolated extramedullary breast relapses of T-ALL. Herein, we report a case of isolated extramedullary breast relapse of T-ALL treated with breathing adapted radiation therapy (BART) using the active breathing control (ABC) system.

CASE SUMMARY

The patient was a 33-year-old female with diagnosis of T-ALL. She received intensive systemic chemotherapy that resulted in complete remission of her disease, and then underwent allogeneic hematopoietic stem cell transplantation. After a 15 mo period without symptoms and signs of progression, the patient presented with palpable masses in both breasts. She complained from severe pain and swelling of the breasts. Imaging workup showed bilateral breast lesions, and diagnosis of breast infiltration by leukemic cells was confirmed after immunohistopathological evaluation. The patient suffering from severe pain, discomfort, and swelling of both breasts due to leukemic infiltration was referred to the Radiation Oncology Department for symptomatic palliation. Whole breast irradiation was delivered to both breasts of the patient with BART using the ABC system. The patient had complete resolution of her symptoms after treatment with BART.

CONCLUSION

BART with the ABC system resulted in complete resolution of the patient's symptoms due to leukemic infiltration of both breasts with T-ALL. This

publication.

Conflict-of-interest statement: The authors state that they have no conflicts of interest.

CARE Checklist (2016) statement: The manuscript was prepared according to the CARE Checklist (2016).

Manuscript source: Invited manuscript

Received: May 17, 2019
Peer-review started: May 20, 2019
First decision: August 2, 2019
Revised: September 4, 2019
Accepted: September 25, 2019
Article in press: September 25, 2019
Published online: November 24, 2019

P-Reviewer: Demonacos C, Gabriel S
S-Editor: Ma RY
L-Editor: Filipodia
E-Editor: Liu MY

contemporary treatment technique should be preferred for radiotherapeutic management of patients with leukemic infiltration of the breasts to achieve effective symptomatic palliation.

Key words: T-cell acute lymphoblastic leukemia; Breast relapse; Breathing adapted radiation therapy; Active breathing control; Case report

Core tip: Although exceedingly rare, leukemic infiltration of the breasts by T-cell acute lymphoblastic leukemia (T-ALL) may manifest as an oncological emergency requiring prompt management. In this case report, we present the first case in the literature treated by breathing adapted radiation therapy using the active breathing control system for management of isolated extramedullary relapse of T-ALL in both breasts.

Citation: Sager O, Dincoglan F, Demiral S, Uysal B, Gamsiz H, Ozcan F, Colak O, Elcim Y, Dirican B, Beyzadeoglu M. Breathing adapted radiation therapy for leukemia relapse in the breast: A case report. *World J Clin Oncol* 2019; 10(11): 369-374
URL: https://www.wjgnet.com/2218-4333/full/v10/i11/369.htm
DOI: https://dx.doi.org/10.5306/wjco.v10.i11.369

INTRODUCTION

A considerable proportion of patients with leukemia suffer from relapse during the course of their disease, mostly in the bone marrow[1]. The central nervous system and testes are frequent locations and sanctuary sites for extramedullary relapses. Involvement of the breast by leukemia is uncommon but may manifest as an oncological emergency requiring prompt management[2-4]. Acute myeloid leukemia constitutes the most common type of acute leukemia in adults, and is also the most common type infiltrating the breasts. Isolated extramedullary relapse of T-cell acute lymphoblastic leukemia (T-ALL) within the breast is exceedingly rare and there is paucity of data in the literature regarding this entity[5-7]. No consensus exists on management of isolated extramedullary breast relapses of T-ALL. Herein, we report a case of isolated extramedullary breast relapse of T-ALL treated with breathing adapted radiation therapy (BART) using the active breathing control (ABC) system.

CASE PRESENTATION

Presenting symptoms and medical history

The patient was a 33-year-old female with diagnosis of T-ALL. Initial laboratory data showed increased leukocyte count of 105 × 10^9 per liter (L), decreased hemoglobin level of 7.8 mg per deciliter (mg/dL), and decreased platelet count of 28 × 10^9/L. She received intensive systemic chemotherapy including L-asparaginase, prednisone, vincristine, and intrathecal methotrexate, hydrocortisone, and cytosine arabinoside, which resulted in complete remission of her disease, and then underwent allogeneic hematopoietic stem cell transplantation. After a 15 mo period without symptoms and signs of progression, the patient presented with palpable masses in both breasts. She complained from severe pain and swelling of the breasts.

Diagnostic workup

Polymerase chain reaction analysis of bone marrow aspirates demonstrated complete allogeneic hematopoietic chimerism, and there were no leukemic lesions at other sites including the bone marrow and cerebrospinal fluid. Imaging workup included bilateral mammography, doppler ultrasonography and breast magnetic resonance imaging (MRI). On ultrasonography, lesions were detected in the upper inner quadrant of the right breast with mixed echo and significant hyperechogenicity. Another lesion was detected in the left breast with mixed echo and significant hyperechogenicity. Doppler ultrasonographic assessment showed vascularization in these breast lesions. Diffusion-weighted and dynamic contrast-enhanced breast MRI revealed significant diffusion restriction and type 2 and 3 contrast patterns. Lesion on

the right breast was heterogeneously hypointense with contrast enhancement. The lesion in the left breast also showed contrast enhancement, and was hypointense on T1 weighted sequencing, and hyperintense on fat suppressed MRI.

FINAL DIAGNOSIS

The patient was referred for biopsy, and diagnosis of breast infiltration by leukemic cells was confirmed after immunohistopathological evaluation. Immunohistopathological assessment revealed presence of small to medium size lymphoblastic cells with narrow cytoplasm and hyperchromatic nuclei. Atypical cells were positive for terminal deoxynucleotidyl transferase, cluster of differentiation 3 (CD3), CD5, and CD34 on immunohistochemical analysis. Paired box gene 5 was weakly positive. Myeloperoxidase, CD10, CD117, and CD20 were negative. The Ki-67 proliferation index was 40%.

MULTIDISCIPLINARY EXPERT CONSULTATION

After multidisciplinary expert consultation, the patient suffering from severe pain, discomfort, and swelling of both breasts due to leukemic infiltration was referred to the Radiation Oncology Department for symptomatic palliation.

TREATMENT

Whole breast irradiation was delivered to both breasts of the patient with BART using the ABC system (Elekta, United Kingdom). Total radiation dose was 50 Gy delivered in 25 daily 2-Gy fractions over 5 wk. The patient was trained for compliance with the ABC system before computed tomography (CT) simulation as per our institutional protocol[8]. Reproducible moderate deep inspiration breath holding (mDIBH) by use of the ABC system has been achieved after the training session, and planning CT images were acquired at the CT-simulator (GE Lightspeed RT, GE Healthcare, Chalfont St. Giles, United Kingdom) at mDIBH. A breast board was used for reproducible positioning and immobilization of the patient at each treatment fraction. After acquisition of the planning CT images, three-dimensional image data sets were transferred to the contouring workstation *via* the network. Delineation of both breast target volumes and critical organs including the spinal cord, heart, and lungs was performed at the Advantage Sim MD simulation and localization software (Advantage SimMD, GE, United Kingdom). Structure sets including the contoured target volumes and critical organs were sent to the treatment planning workstation. Radiation treatment planning for whole breast irradiation of both breasts was performed by using PrecisePLAN treatment planning system (PrecisePLAN, Elekta, United Kingdom). BART was delivered at the linear accelerator (Synergy, Elekta, United Kingdom) under image guidance for setup verification using electronic portal imaging device (Iview, Elekta, United Kingdom) and kilo-voltage cone beam CT (X-ray volumetric imaging, Elekta, United Kingdom).

OUTCOME AND FOLLOW-UP

Compliance of the patient with treatment procedure was excellent and there was no need for any treatment breaks. The patient had complete resolution of her symptoms after treatment with BART. The timeline of the disease course is shown in Table 1. Axial CT images of the patient before and after treatment with BART are shown in Figures 1 and 2, respectively.

DISCUSSION

Literature review

There is paucity of data regarding extramedullary relapse of ALL in the breast. Although rare, extramedullary relapse should be vigilantly considered in differential diagnosis of a breast lump when a history of leukemia is present[9,10].

As a local treatment modality, radiation therapy has been judiciously used for management of extramedullary leukemia relapse in sanctuary sites such as the CNS

Table 1 Timeline of the disease course

Timeline of the disease course	
Initial diagnosis of T-ALL	May 2017
Complete remission after chemotherapy	July 2017
Allogeneic hematopoietic stem cell transplantation	August 2017
Presentation with palpable masses in both breasts	November 2018
Diagnosis of extramedullary breast relapse of T-ALL	December 2018
Bilateral whole breast irradiation with BART using ABC	January 2019
Complete resolution of symptoms and breast lesions	February 2019

T-ALL: T-cell acute lymphoblastic leukemia; BART: Breathing adapted radiation therapy; ABC: Active breathing control.

and testes[11-13]. Regarding isolated extramedullary relapses of ALL within the breast, there is no consensus on standard management. Nevertheless, complete resolution of breast lesions by use of irradiation has also been reported in other studies consistent with our findings[14-16]. Future trials are clearly needed to shed light on optimal management of isolated extramedullary relapses of ALL in the breast.

Discussion

Extramedullary relapse of T-ALL in the breast is exceedingly rare. To the best of our knowledge, management of leukemic infiltration of both breasts by T-ALL by use of BART has not been previously addressed in the literature. BART has been the primary mode of radiotherapeutic management of breast cancer in our department given the reported dosimetric benefits and significantly improved normal tissue sparing with incorporation of breath holding at moderate deep inspiration during treatment simulation and delivery[8,17,18].

Briefly, mDIBH with the ABC system was developed for management of respiratory motion for thoracoabdominal tumors and has been used for this purpose in both conventionally fractionated radiotherapy regimens and Stereotactic Body Radiation Therapy applications[8,17-21]. In addition to respiratory motion management, an additional benefit of mDIBH with the ABC system for breast cancer includes minimizing exposure of the heart particularly for left-sided breast cancer patients along with improved sparing of other critical organs, which has been supported in previous studies[8,17,18].

Given the benefits of BART, this contemporary technique was adapted for management of our patient with bilateral breast lesions and led to complete resolution of her symptoms. Bilateral whole breast irradiation using BART for leukemic infiltration of both breasts with T-ALL has not been subject to any previous reports. However, there is no standard management in the setting of leukemic infiltration of both breasts with T-ALL, and treatment decisions regarding management of this exceedingly rare entity are individualized based on patient and tumor characteristics along with institutional experiences. Incorporation of contemporary techniques such as BART at mDIBH with the ABC system may offer improved radiotherapeutic management of these patients, particularly in the setting of bilateral breast irradiation.

CONCLUSION

BART with the ABC system resulted in complete resolution of the patient's symptoms due to leukemic infiltration of both breasts with T-ALL. This contemporary treatment technique should be preferred for radiotherapeutic management of patients with leukemic infiltration of the breasts to achieve effective symptomatic palliation.

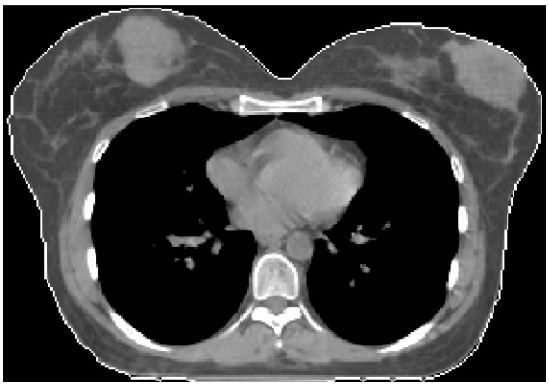

Figure 1 Axial computed tomography images of the patient showing bilateral breast lesions before breathing adapted radiation therapy.

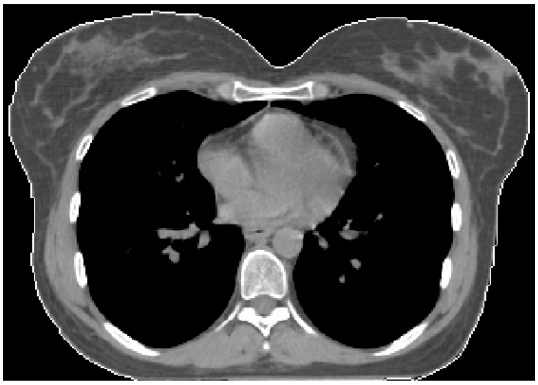

Figure 2 Axial computed tomography images of the patient showing complete resolution of bilateral breast lesions after breathing adapted radiation therapy.

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World Journal of Clinical Oncology

Submit a Manuscript: https://www.f6publishing.com

World J Clin Oncol 2019 November 24; 10(11): 375-381

DOI: 10.5306/wjco.v10.i11.375

ISSN 2218-4333 (online)

CASE REPORT

Radiation-induced malignant rhabdoid tumour of the hypothalamus in an adult: A case report

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Author contributions: Ng PM and Low PH reviewed the literature and contributed to manuscript drafting; Wong ASH and Liew DNS were responsible for the revision of the manuscript for important intellectual content; all authors issued final approval for the version to be submitted.

Informed consent statement: Informed written consent was obtained from the patient's parent for publication of this report and any accompanying images.

Conflict-of-interest statement: The authors declare that they have no conflicts of interest.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

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Abstract

BACKGROUND

Rhabdoid tumours of the central nervous system are highly malignant and extremely rare in adults. To the best of our knowledge, only 87 cases of malignant rhabdoid tumour have been reported to date, inclusive of 4 cases with presumed radiation-induced aetiology. We report a case of malignant rhabdoid tumour in an adult with presumed radiation-induced aetiology to enrich the armamentarium of this disease entity, which may have some implications for early diagnosis and treatment of this rare disease in the future.

CASE SUMMARY

A 27-year-old male, who was exposed to cranial irradiation at the age of 4 years as part of the treatment for acute lymphoblastic leukaemia, presented with symptoms of raised intracranial pressure for one week. Brain magnetic resonance imaging revealed a heterogeneously enhancing lesion at the hypothalamus. Stereotactic biopsy was performed. Histopathological examination of the lesion showed malignant rhabdoid tumour. The disease progressed rapidly, with manifestation of leptomeningeal spread. He was started on craniospinal irradiation but treatment was suspended after 5.4 Gy, as he developed myelosuppression. His clinical condition deteriorated rapidly, and he succumbed to his illness within 2 mo.

CONCLUSION

This fifth case of radiation-induced central nervous system rhabdoid tumour re-enforces the aggressive nature of this disease with poor prognosis.

Key words: Malignant rhabdoid tumour; Atypical teratoid rhabdoid tumour; Radiation induced malignancy; Case report

Core tip: Malignant rhabdoid tumours of the central nervous system are highly

Manuscript source: Unsolicited manuscript

Received: May 23, 2019
Peer-review started: May 23, 2019
First decision: August 2, 2019
Revised: October 10, 2019
Accepted: October 15, 2019
Article in press: October 15, 2019
Published online: November 24, 2019

P-Reviewer: Gheita TA, Yang LY
S-Editor: Ma RY
L-Editor: A
E-Editor: Liu MY

malignant, with a grave prognosis. Occurrence in adults is extremely rare. Due to the paucity of available data, treatment recommendations for adults are derived mainly from paediatric data. Despite being a dismal disease, prognosis in children has been more encouraging recently due to the continuous refinement of treatment strategies. We report a case of malignant rhabdoid tumour in an adult with presumed radiation-induced aetiology, with the hope to enrich the armamentarium of this disease entity and provide some implications for early diagnosis and treatment of this disease in the future.

Citation: Ng PM, Low PH, Liew DNS, Wong ASH. Radiation-induced malignant rhabdoid tumour of the hypothalamus in an adult: A case report. *World J Clin Oncol* 2019; 10(11): 375-381
URL: https://www.wjgnet.com/2218-4333/full/v10/i11/375.htm
DOI: https://dx.doi.org/10.5306/wjco.v10.i11.375

INTRODUCTION

The advancement in therapeutic measures in the oncology field has led to a significant improvement in the overall survival of cancer patients. Hence, we are facing more complications from those therapeutic measures, including an increase in the number of radiation-induced malignancies. Malignant rhabdoid tumour (MRT) of the central nervous system (CNS) in adult is very rare, and the literature available consists mainly of case reports or series. Despite the rarity of this disease entity, 4 cases[1-4] of presumed radiation-induced MRT in the brain have been reported to date. We present herein a case of hypothalamic tumour in an adult patient diagnosed with MRT following prophylactic irradiation for acute lymphoblastic leukaemia during childhood.

CASE PRESENTATION

Chief complaints

A 27-year-old male presented with headache, vomiting and blurring of vision for 1 wk duration.

History of present illness

The patient's headache was of gradual onset, throbbing in nature, worse in the morning with associated projectile vomiting and blurring of vision. The headache was relieved temporarily by analgesia but progressively worsened over the course of a week.

History of past illness

The patient had history of acute lymphoblastic leukaemia at the age of four and was treated according to the Berlin-Frankfurt-Munster Protocol.

Physical examination

Neurological examination on the day of admission revealed bilateral reduction in visual acuity. Visual acuity for the right eye was light perception and for the left eye was 6/6. No other neurological deficit was noted. Systemic examinations were unremarkable.

Laboratory examinations

Blood investigation findings were normal.

Imaging examinations

Magnetic resonance imaging of the brain revealed a heterogeneously enhanced hypothalamic tumour (Figure 1). The lesion measured 2 cm × 1.5 cm, located mainly at the hypothalamus with extension into the optic chiasm. No pituitary stalk and pituitary gland involvement was detected.

Further diagnostic work-up

Stereotactic biopsy of the tumour was performed. Histopathological examination of the specimen showed focus of tumour infiltration that displayed rhabdoid

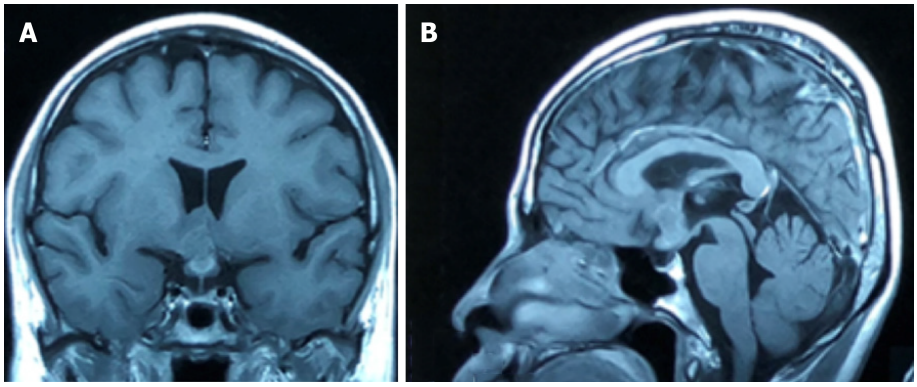

Figure 1 Magnetic resonance imaging of the brain, T1-weighted gadolinium-enhanced. Coronal (A) and sagittal (B) view showing a heterogeneously enhanced lesion at the hypothalamic region with extension into the optic chiasm.

morphology (Figure 2). Nuclei were eccentrically placed, hyperchromatic and pleomorphic with coarse chromatin. There was an ample amount of eosinophilic cytoplasm. Mitotic figures were seen. The cells stained positive for vimentin, cytokeratin (CK) AE1/AE3, glial fibrillary acidic protein (GFAP), cluster of differentiation (CD) 68 and CD138. Synaptophysin, human melanoma black 45, CK7, CK20, desmin, smooth muscle actin, CD79, CD30, terminal deoxynucleotidyl transferase, placental alkaline phosphatase, and leucocyte common antigen were negative upon staining. Ki67 was more than 20%.

FINAL DIAGNOSIS

The final diagnosis of the presented case was MRT of the CNS.

TREATMENT

The patient's clinical condition deteriorated rapidly, with manifestation of leptomeningeal dissemination. He lost his vision within 5 d and developed multiple cranial neuropathies over the subsequent week. This started off with right eye ptosis, followed by bilateral lateral gaze palsy, loss of the left frontal furrow upon upward gaze with loss of the left nasolabial fold and drooping of the left angle of the mouth. His voice became softer, and he coughed upon swallowing both liquid and food. His tongue showed fasciculation with deviation to the right. This was followed by progressive bilateral lower limb weakness over the next week. The spinal magnetic resonance imaging showed leptomeningeal spread. Lumbar puncture was performed, and cerebrospinal fluid analysis revealed dispersed cells with rhabdoid features. The treatment plan was to administer 36 Gy of craniospinal radiation (20 fractions). However, treatment was halted after 5.4 Gy as he developed myelosuppression.

OUTCOME AND FOLLOW-UP

The patient's general condition deteriorated rapidly after the radiotherapy was halted, and he succumbed to his illness within 2 mo from the onset of the illness.

DISCUSSION

MRTs of the brain were first described in 1987[5]. They have been characterised by diffuse growth of rhabdoid cells with typical paranuclear, glassy eosinophilic inclusions. Their nuclei are eccentrically placed, vesicular and with occasional prominent nucleoli, and mitosis is commonly found[6,7].

According to the World Health Organization classification of tumours of the CNS[8], MRT of the CNS with polyphenotypic (epithelial, mesenchymal, neuroendocrine) features by histology or immunohistochemical staining can be categorised into atypical teratoid rhabdoid tumour (ATRT) or CNS embryonal tumour with rhabdoid features based on their integrase interactor 1 (INI 1) status. In ATRT, there must be

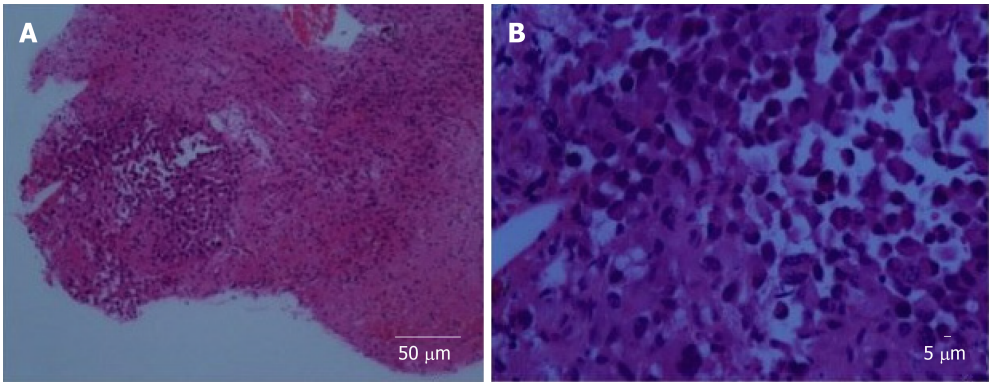

Figure 2 Histopathological examination. A: Glial tissue infiltrated by a focus of singly dispersed malignant cells (40 ×); B: At high magnification, the lesion is composed of rhabdoid cells with hyper chromatic nuclei, coarse chromatin and abundant eosinophilic cytoplasm (400 ×).

SMARCB1 (INI1) or SMARCA4 (BRG1) inactivation. Those with expression of SMARCB1 (INI1) and SMARCA4 (BRG1) or in which SMARCB1 and SMARCA4 status cannot be confirmed fall into the group of CNS embryonal tumour with rhabdoid features, despite having the same pathological features as ATRTs.

Eighty-seven cases of MRT of the brain in adult has been reported,, with 39 of them located at midline and 47 cases off midline. The location was not mentioned in one case. For those located at the midline, 31 cases of sellar and suprasellar tumour were reported. Another 8 cases were located at the pineal region. Our case is the first in the literature to report an MRT located at the hypothalamus. This supports the hypothesis of Dardis *et al*[9], which states that the residual undifferentiated ectoderm in the circumventricular organ can be an origin for this tumour.

The appearances of rhabdoid tumour in the lung and ileum 20 years after radiation therapy (RT) for Wilms' tumour have been reported by Litman *et al*[10], raising the possibilities of radiation-induced rhabdoid tumour. Four adult cases of presumed RT-induced MRT of the CNS have been reported in the literature[1-4]. The clinicopathological and imaging features of these cases and our case are summarised in Table 1, Table 2 and Table 3. Genetic analysis was performed in 1 of the 5 cases, which demonstrated loss of both SMARCB1 alleles at chromosome 22. Four cases showed inactivation of INI 1. The average age at the time of previous irradiation was 5.4 years, with a mean total radiation dose of 28 Gy and an average latency period of 23 years (Table 4). Overall prognosis is poorer compared to non-RT-induced MRT in adults, with a mean survival of 12 mo compared to 38 mo in the non-RT-induced group[1-4].

Imaging features for MRT of the CNS are non-specific. A combination of intratumoral haemorrhage, peripherally localised cysts, high cellularity seen as low T2 and apparent diffusion coefficient signal, as well as band-like or wavy enhancement can be seen. Around 15% of patients display meningeal dissemination at diagnosis[11]. For the 5 cases of presumed RT-induced MRT, all of them were located at the supratentorial compartment. Two cases were located at midline, and three cases were located off midline. Peritumoral oedema was more pronounced in the 3 cases located off midline, and peripheral tumour cysts were found in those 3 cases only. All cases demonstrated heterogenous contrast enhancement, with 3 of them showing the characteristic band-like enhancement. Leptomeningeal spread was present in 1 out of the 5 cases during the first presentation.

In the present case, the diagnosis of ATRT was suspected initially, but due to the rarity of this disease in adult this differential was deprioritized. A wide range of immunohistochemical stains were employed to exclude other possibilities first. Because of this, we found that our case was positive for CD138, which has never been reported for other cases in the past. CD138 is involved in molecular pathways that are dysregulated during carcinogenesis, and it can be an attractive target for immunotherapy in cancer treatment[12]. Other immunohistochemical stains that were positive in our case included vimentin, CKAE1/AE3, CD68, and GFAP. Staining for synaptophysin, human melanoma black 45, CK7, CK20, desmin, leucocyte common antigen, CD79, CD30, terminal deoxynucleotidyl transferase, and placental alkaline phosphatase were negative. Ki67 was increased (more than 20%).

GFAP staining in MRT of the CNS has been found to be strongly correlated with leptomeningeal spread and predicts a worse prognosis[9]. Our case further re-enforces this evidence, as the patient's specimen was positive for GFAP staining and he manifested leptomeningeal spread early in the course of his disease with rapid

Table 1 Summary of patients, symptoms, treatments, and outcomes of radiation-induced malignant rhabdoid tumour

Case	Age (yr)	Gender	Symptom	Location	Treatment	Survival	Outcome
Padua *et al*[1]	17	Male	Headache	Right frontal	Surgery (partial resection), radiotherapy	15 mo	Alive
Kuge *et al*[2]	20	Female	Severe headache, increased ICP symptoms	Pineal	Surgery (biopsy), gamma knife radiosurgery	27 mo	Died
Gorayski *et al*[3]	58	Female	Headache, recurrent syncopal events, behavioural changes	Right parietotemporal	Surgery (gross total resection), radiotherapy	20 mo	Died
Oliveira *et al*[4]	22	Female	headache, nausea, vomiting	Frontal	Surgery (partial resection)	4 d	Died
Our case	27	Male	Headache, vomiting, visual disturbance	Hypothalamus	Surgery (biopsy), radiotherapy	2	Died

ICP: Intracranial pressure.

deterioration.

Multimodal therapy has been the proposed treatment strategy for MRT, by combining RT and chemotherapy following surgical resection[13,14]. Improved disease survival has been shown in patients given a total RT dose of more than 50 Gy[15]. However, treatment strategies in the group of patients with a history of irradiation might need to be modified as re-irradiation can expose them to the risk of central nervous toxicity. The impact of toxicity depends on the dose, volume and time between exposures. Hence, re-irradiation in a patient with a history of RT requires tedious planning and good patient selection. Consideration should be given to other modes of treatment, such as stereotactic radiosurgery, which provide more precise and targeted tissue damage[16], or to local conformal proton therapy, which has shown encouraging results[17]. For candidates not suitable for re-irradiation, high-dose chemotherapy with autologous stem cell rescue may also be an option[18].

CONCLUSION

In summary, MRT of the CNS in adults remains a rare disease with an aggressive course and poor prognosis. Treatment recommendations for adults have been derived from paediatric data, due to the paucity of data available from adults. Despite being a dismal disease, prognosis in children has been more encouraging recently compared to 10 years ago, due to the continuous development and refinement of treatment strategies. We report a case of MRT in an adult with presumed radiation-induced aetiology, with the hope of enriching the armamentarium of this disease entity, which may have some implications for early diagnosis and treatment of this rare disease in the future.

Table 2 Summary of immunohistological findings of radiation-induced malignant rhabdoid tumour

Case	Padua *et al*[1]	Kuge *et al*[2]	Gorayski *et al*[3]	Oliveira *et al*[4]	Our case
Vimentin	+	+	+	+	+
EMA	+	+	+	+	-
SMA	NA	+	+	NA	-
INI 1	-	-	-	-	NA
GFAP	-	-	-	+	+
NFP	NA	-	+	+	NA
S100	NA	+	-	NA	NA
CK:	-	NA	-	NA	
CKAE1/AE3					+
CK7					
CK20					
Chromosome 22q deletion	NA	NA	NA	+	NA
Desmin	-	NA	-	NA	-
LCA	-	NA	-	NA	-
Ki67	NA	7.8%	NA	NA	>20%
Others (stain positive)	Neuron-specific enolase	NA	CD99	NA	CD138, CD68,
Others (stain negative)	CD99, Tdt, myeloperoxidase	NA	HMB45, CD34, CD31, CD10, PLAP, MelanA, MYOD1, myogenin, chromogranin, p63	NA	Synaptophysin, HMB45, CD117, CD79, CD30, Tdt, PLAP

CD: Cluster of differentiation; CK: Cytokeratin; EMA: Epithelial membrane antigen; GFAP: Glial fibrillary acidic protein; HMB: Human melanoma black; INI 1: Integrase interactor 1; LCA: Leukocyte common antigen; MYOD: Myoblast determination protein; NA: Not applicable; NFP: Neurofilament protein; PLAP: Placental alkaline phosphatase; SMA: Smooth muscle actin; Tdt: Terminal deoxynucleotidyl transferase.

Table 3 Imaging features of radiation-induced malignant rhabdoid tumour

MRI	Padua *et al*[1]	Kuge *et al*[2]	Gorayski *et al*[3]	Oliveira *et al*[4]	Our case
Oedema	Yes	No	Yes	Yes	No
Peripheral cyst	Yes	No	Yes	Yes	No
Calcification	Yes	No	Yes	Yes	No
Contrast enhancement	Heterogenous	Heterogenous	Heterogenous, band-like	Heterogenous, band-like	Heterogenous, band-like
T2 signal	NA	NA	Hyperintense	NA	Hyperintense
FLAIR	NA	NA	Hyperintense	NA	Hyperintense
Leptomeningeal spread at first presentation	No	No	No	No	Yes
CT	Mix density: iso to hyperdense with foci of calcification and necrosis	Isodense	Mix density: isodense with foci of calcification and cyst	NA	Isodense to hyperdense

CT: Computed tomography; MRI: Magnetic resonance imaging; NA: Not available.

Table 4 Previous treatment details for radiation-induced malignant rhabdoid tumour

Case	Padua *et al*[1]	Kuge *et al*[2]	Gorayski *et al*[3]	Oliveira *et al*[4]	Our case
Latency period in yr	11	18	55	10	23
Age of previous RT in year	6	2	3	12	4
Dose of previous RT	NA	24 Gy	35 Gy	34 Gy	20 Gy
Reason for previous RT	Acute lymphoblastic leukaemia treatment: prophylactic cranial irradiation	Acute lymphoblastic leukaemia treatment: prophylactic cranial irradiation	Right ear sarcoma	Subtotal surgical removal of craniopharyngioma	Acute lymphoblastic leukaemia treatment: prophylactic cranial irradiation

RT: Radiation therapy.

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