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Clinicopathological and genetic characterization of radiotherapy-induced undifferentiated pleomorphic sarcoma following breast cancer: a case series of three tumors and comprehensive literature review

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Abstract

Aims Compared to primary breast sarcoma (BSs), radiotherapy-induced sarcoma (RIS) is a less frequent type of secondary breast sarcoma. Undifferentiated pleomorphic sarcoma (UPS) is an even rarer occurrence within the RIS category. This study aimed to present the clinicopathologic and molecular features of breast radiotherapy-induced UPS.

Methods A retrospective study was conducted at the Third Affiliated Hospital of Soochow University to analyze three patients with radiation-induced undifferentiated pleomorphic sarcoma (UPS) following breast cancer, spanning from 2006 to 2023. The clinical and pathological variables were extracted from the medical records, while immunohistochemistry was employed to analyze the immunophenotypes of these tumors. Genomic characteristics were assessed through DNA and RNA sequencing techniques. Another 15 cases from the literature were also reviewed to better characterize the tumor.

Results The affected areas encompass the chest wall and breasts, with an incubation period ranging from 6 to 17 years. The tumor cells exhibit pleomorphism and demonstrate a high degree of pathological mitosis. Notably, two cases displayed an accelerated disease progression, characterized by recurrent tumors and metastases occurring within short intervals of 48 and 7 months respectively subsequent to the initial diagnosis. The two prevailing identified genes were *TP53* (2/3, 66.7%) and *RB1* (1/3, 33.3%). Through analysis of somatic copy number variation (CNV), it was discovered that two oncogenes, *MCL1* (1/3, 33.3%) and *MYC* (1/3, 33.3%), had experienced gains in CNV. The Tumor Mutational Burden (TMB) values for case 1, case 2, and case 3 were 5.9 mut/Mb, 1.0 mut/Mb, and 3.0 mut/Mb, respectively. Moreover, the analysis of RNA-NGS (next-generation sequencing) revealed the presence of a novel gene fusion, named *COL3A1-GULP1*, in case 2.

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Conclusions Based on our thorough analysis of research findings and previous reports, it is evident that radiotherapy-induced UPS exhibits a highly diverse and frequently severe clinical and biological behavior. Identifying tumor formation using genome sequencing can help understand its biological behavior and determine personalized treatments.

Keywords Radiotherapy-induced sarcoma (RIS), Undifferentiated pleomorphic sarcoma (UPS), Poor prognosis, *TP53*, *RB1*, *COL3A1-GULP1*

Introduction

Breast sarcoma (BS) is an extremely uncommon form of breast tumor, much rarer than cancer, and makes up less than 1% of all breast malignancies and less than 5% of all sarcomas [1]. The majority of sarcomas are primary and typically occur in individuals aged between 55 and 59 years [2]. After breast-conserving surgery, adjuvant radiation therapy is an important part of breast cancer treatment, but it can also lead to certain issues. Sarcomas can arise in areas that have undergone radiation therapy, such as the breast, chest wall, axilla, sternum and supraclavicular region [3]. Although uncommon, this is a recognized complication of radiotherapy for breast cancer.

Radiotherapy-induced sarcomas (RISs) were first identified in 1948 and defined in 1971 to include a minimum incubation period of 3 years prior to the newly diagnosed sarcomas, occurs in the radiating region of the previous tumor, and the primary tumor is histologically different from the sarcoma [3]. The cumulative incidence of RIS is 0.3% at 15 years after radiotherapy which is rarer than primary BSs, of which, the most common were angiosarcoma, morphologically identical to primary BSs [3, 4]. Undifferentiated pleiomorphic sarcoma (UPS) accounts for 10.5%–24% of primary BSs, but there is no definite data on the incidence of secondary BSs [3, 5].

Primary UPS is a highly aggressive tumor with a high rate of local recurrence and distant metastasis, as is in the breast [2, 6–9]. Although radiotherapy-induced UPS is rare, cases of high aggressiveness and poor prognosis have been reported [4, 9]. Studies that did not focus on particular sites have indicated that sarcomas caused by radiotherapy may be more aggressive and have a poorer prognosis compared to primary sarcomas [3, 10, 11]. Currently, there is a lack of comparative reports on the biological behavior between primary and secondary UPS of the breast. In terms of radiotherapy-induced UPS in the breast being rare, only a limited number of case reports exist, and treatment options are primarily based on extrapolation from similar sarcomas found in other anatomical regions [2, 12]. The advent of next-generation sequencing (NGS) technology has significantly enhanced our comprehension of tumor pathogenesis and biological behavior. It is noteworthy that gene sequencing has unveiled substantial disparities in the genomic constitution between primary breast angiosarcoma and radiotherapy-induced angiosarcoma, which underlie their divergent biological behaviors.

Our study presents a comprehensive report on three patients who developed radiation-induced UPS in the breast and chest wall, diagnosed based on the specified criteria. The study provides detailed analysis of the clinicopathological characteristics of radiotherapy-induced UPS following breast cancer, aiming to enhance our understanding of its pathogenesis and biology, as well as identify potential therapeutic targets.

Materials and methods

Case selection

A retrospective search of the pathology database at the Third Affiliated Hospital of Soochow University for radiation-induced UPS of the breast was carried out from 2006 to 2023 year. All available slides and blocks of the three known breast cancer patients who developed sarcoma after surgery were retrieved from the Department of Pathology, the Third Affiliated Hospital of Soochow University. Finally, three cases with the diagnosis of radiotherapy-induced UPS were identified. Patient history, treatment, and outcomes were obtained from institutional medical records, managed healthcare providers, and telephone follow-ups. Before the study, all patient samples were anonymized and used in alliance with the ethical rules and regulations presented in the Declaration of Helsinki.

Immunohistochemistry (IHC) staining

IHC analysis was performed for AE1/AE3 (ZSGB- BIO, Beijing, China), EMA (ZSGB- BIO, Beijing, China), smooth-muscle actin (SMA) (MXB Biotechnology, Fujian, China), desmin (MXB Biotechnology, Fujian, China), h-caldesmon (MXB Biotechnology, Fujian, China), MyoD1(MXB Biotechnology, Fujian, China), Myogenin (MXB Biotechnology, Fujian, China), CD34 (ZSGB- BIO, Beijing, China), S-100 (ZSGB- BIO, Beijing, China), Sox10 (ZSGB- BIO, Beijing, China), estrogen receptor (ER) (Ventana, Tucson, Arizona, USA), progesterone receptor (PR) (Ventana, Tucson, Arizona, USA), HER2/neu (Ventana, Tucson, Arizona, USA), and Ki-67 (Ventana, Tucson, Arizona, USA). After dewaxing and hydration, 4 μm sections from formalin-fixed paraffin-embedded tissue were treated by an immunohistochemical automatic staining machine according to the protocol

provided by the Benchmark XT system, and there were positive and negative tissues for comparisons in every case.

DNA-NGS

For DNA sequencing, formalin-fixed paraffin-embedded (FFPE) samples, five 10 μm tumor slices were used for DNA extraction using the QIAamp DNA FFPE Kit (QIAGEN, Valencia, CA, USA) following the manufacturer's instructions. DNA quality was assessed by spectrophotometry with absorbance at 230, 260, and 280 nm, and quantified by Qubit 2.0. Target-enriched libraries (481-cancer-relevant genes, Geneseeq Technology Inc.) were sequenced on the HiSeq4000 platform (Illumina) with 2×150 bp pair-end reads. Sequencing data were demultiplexed by bcl2fastq v2.19, analyzed by Trimmomatic to remove low-quality (quality < 15) or N bases, and mapped to the reference hg19 genome (Human Genome version 19) using the Burrows-Wheeler Aligner. The data analysis was conducted in accordance with the previously described methodology [13].

RNA-NGS

Total RNA from FFPE samples was extracted using miRNeasy FFPE kit (QIAGEN, Valencia, CA, USA). Ribosomal RNA was depleted using KAPA Stranded RNA-seq Kit with RiboErase (HMR) (KAPA Biosystems). Base calling was performed on bcl2fastq v2.16.0.10 (Illumina, Inc.). STAR (version 2.5.3a) is used for transcriptome mapping followed by isoform and gene level quantification performed by RSEM (version 1.3.0). Differential expression analysis was conducted by R packages DESeq2 (version 1.16.1) and edgeR (version 3.18.1). Corresponding volcano plots and heatmaps were generated by in-house R scripts. GO and KEGG enrichment analysis was performed by ClusterProfiler (version 3.4.4). Fusion Catcher (version 0.99.4e) was used with parameters (aligners blat, bowtie2, star, otherwise default parameter) which uses Bowtie aligner to perform both transcriptome and genome mapping and then respectively uses BLAT aligner, bowtie2 aligner, and star aligner to further map unmapped reads and count fusion supporting evidence (RNA-seq Kit, Geneseeq Technology Inc.). Meanwhile, we analyze fusion using blast by in-house script. The combined fusion results from all tools were manually reviewed on IGV for confirmation.

Results

Clinical findings

Case 1

A chest wall lump that was rapidly expanding was brought to the attention of the breast surgery department by a 57-year-old female. Reviewing her medical history reveals that she was diagnosed with breast cancer 17 years prior, at which point she underwent a left mastectomy and ipsilateral axillary dissection. She underwent radiotherapy (Synchronous radiotherapy: 50 Gy in 25 fractions on the chest wall and 50 Gy in 25 fractions on the lymphatic nodes) and chemotherapy following the operation. The initial opinion was that the lesion was a return of breast cancer because it was hard and immobile, located in the chest wall just below the surgical incision. Computed tomography (CT) imaging revealed a 2.4*0.9 hypoechoic mass subcutaneously on the left chest wall, with an uneven border and burr change (Fig. 1A). The positron emission tomography (PET)/computed tomography (CT) scan revealed an increase in FDG metabolism in the left chest wall (inferior ensisternum), while taking into consideration breast cancer recurrence. Following an excisional biopsy, it was discovered that the patient had UPS. The postoperative pathology was the same even though the patient underwent tumor removal

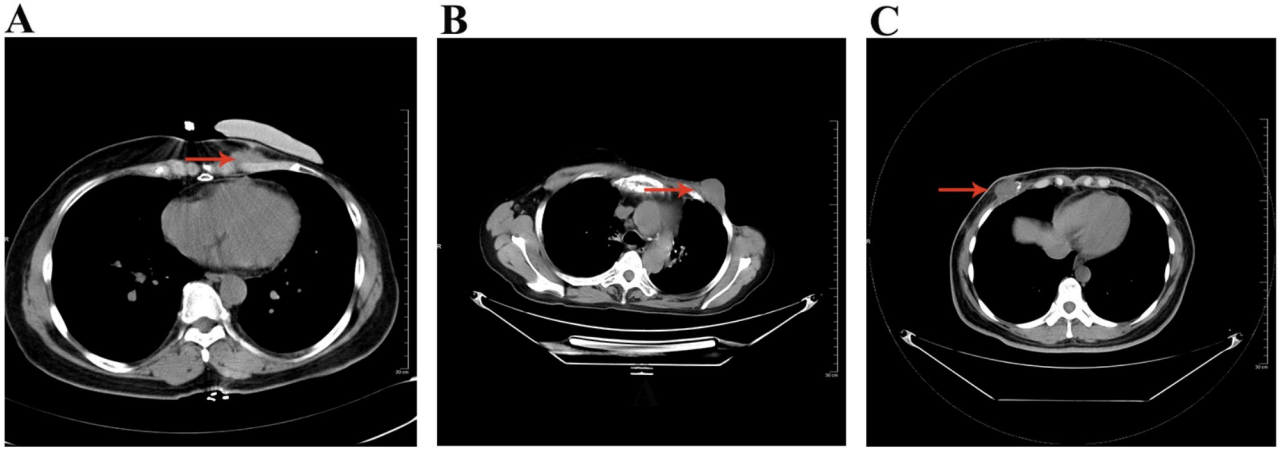

Fig. 1 Imaging studies revealed a soft tissue mass (red arrows) corresponding to the palpable lesion on CT Chest. (**A**) hypoechoic mass subcutaneously on the left chest wall; (**B**) soft tissue nodular in left chest wall; (**C**) a mass in the lower quadrant of the right breast

at a different facility. The patient did not receive any adjuvant therapy and recurred 48 months follow-up in the chest wall. At a different facility, the tumor was removed once more without adjuvant therapy, and a 20-month follow-up revealed no progression.

Case 2

A 50-year-old female who had been experiencing a two-month-old tumor in her left chest wall presented to the breast surgery department. A 5.0*3.0 cm hard mass was found in the left chest wall during the examination, and the left breast was missing. According to the patient's medical history, she underwent a modified radical mastectomy for breast cancer on the left breast 14 years ago along with adjuvant radiotherapy (Synchronous radiotherapy: 50 Gy in 25 fractions on the chest wall and 50 Gy in 25 fractions on the lymphatic nodes), chemotherapy, and endocrine therapy. After the left breast cancer was removed, a CT scan revealed that the left breast was absent. Additionally, a nodular soft tissue shadow with a maximum layer of 4.1*3.7 cm and an unclear boundary was seen on the left chest wall (Fig. 1B). The PET/CT scan showed no additional lesions apart from elevated FDG uptake on the left chest wall. A core needle biopsy (CNB) was then performed on the patient and UPS was diagnosed. Tumor resection was performed at another facility, and the postoperative pathology was the same. Up to now 60 months, no recurrence or metastasis has been observed in this patient. A month after the surgery, the patient was diagnosed with cervical cancer and has since undergone chemotherapy and immunotherapy.

Case 3

A 32-year-old female patient incidentally detected a palpable mass in her right breast. Given her history of previous breast-conserving surgery for breast cancer on the same side six years ago, she presented to the Department of Breast Surgery for further evaluation. A mass measuring approximately 3.0*2.0 cm centimeters was palpable at the site of the original surgical incision on the right breast, with no associated nipple discharge or erosion of the nipple and areola, and absence of enlarged axillary lymph nodes. Ultrasound showed a solid mass in the right breast, and CT showed a mass in the lower quadrant of the right breast (Fig. 1C), considering the possibility of recurrence. Following CNB, the patient was diagnosed with a spindle cell tumor containing pleomorphic cells, indicating a tendency towards sarcoma based on immunohistochemistry results. A comprehensive review of the patient's medical history revealed that she underwent breast-conserving surgery for breast cancer six years ago and subsequently received chemotherapy, radiotherapy (Synchronous radiotherapy:45 Gy to the breast in 25 fractions, 60 Gy to the boost in 25 fractions, and 48 Gy were applied to the lymphatic nodes), and anti-Her2-targeted therapy. The disease onset is situated within the radiation field of the breast adjacent to the initial breast-conserving incision. A simple mastectomy was performed, followed by a postoperative pathological report indicating UPS. The PET/CT examination simultaneously excluded the possibility of a metastatic tumor. After the surgical procedure, the patient proceeded to another medical facility for a consultation, wherein the pathological findings remained consistent. No adjuvant therapy was administered after surgery, and supraclavicular metastases emerged at 7 months of follow-up.

Histopathologic and IHC features

Histologically, the tumor group exhibited a heterogeneous high-grade sarcoma with pleomorphic nuclei and visible pathological mitosis. The case 1 exhibited a dense arrangement of adipose fusiform and oval neoplastic cells interspersed with pleomorphic neoplastic cells containing numerous mitotic figures (Fig. 2A and B). The tumor cells exhibit diffuse arrangement with abundant and eosinophilic cytoplasm, coarse nuclear chromatin, discernible nucleoli, and a profusion of small vessels (Fig. 2C and D). The tumor in case 2 exhibited a composition of round, oval, and spindle cells with vacuolar or pale cytoplasm and coarse nuclear chromatin (Fig. 3A and B). Additionally, the presence of giant pleomorphic tumor cells was observed along with easily identifiable mitotic figures (Fig. 3C and D). The histomorphology of case 3 exhibited heterogeneity, with spindle-shaped cells present in some areas and relatively sparse cells with rough chromatin (Fig. 4A and F). Nucleoli were visible in some cells, and a large number of collagen fibers were observed between the cells (Fig. 4A and F). In other parts, there were relatively dense cells that featured prototype oval giant tumor cells with rough chromatin (Fig. 4G and H). The corresponding metastases exhibit high density and a significant presence of tumor giant cells (Fig. 4I and L). Considering that all the patients had a history of breast cancer, various differential diagnoses were taken into account, including metaplastic carcinoma, malignant phyllodes tumor, malignant melanoma of the breast, and high-grade sarcoma of another type of soft tissue. Immunohistochemistry (IHC) was performed to differentiate these possibilities. All the immunohistochemical parameters, including AE1/AE3, EMA, CK7, CK8/18, smooth muscle actin (SMA), desmin, h-caldesmon, CD34, CD31, S-100 protein, Sox10, estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor 2 (HER2), and Ki-67 index were evaluated in all the three cases encompassing both the primary and metastatic lesions of case 3. A high Ki-67 index was observed in all three cases (Figs. 2E, 3E and 4M and N). Except for SMA which showed focal positivity in case 2 (Fig. 3F) and the

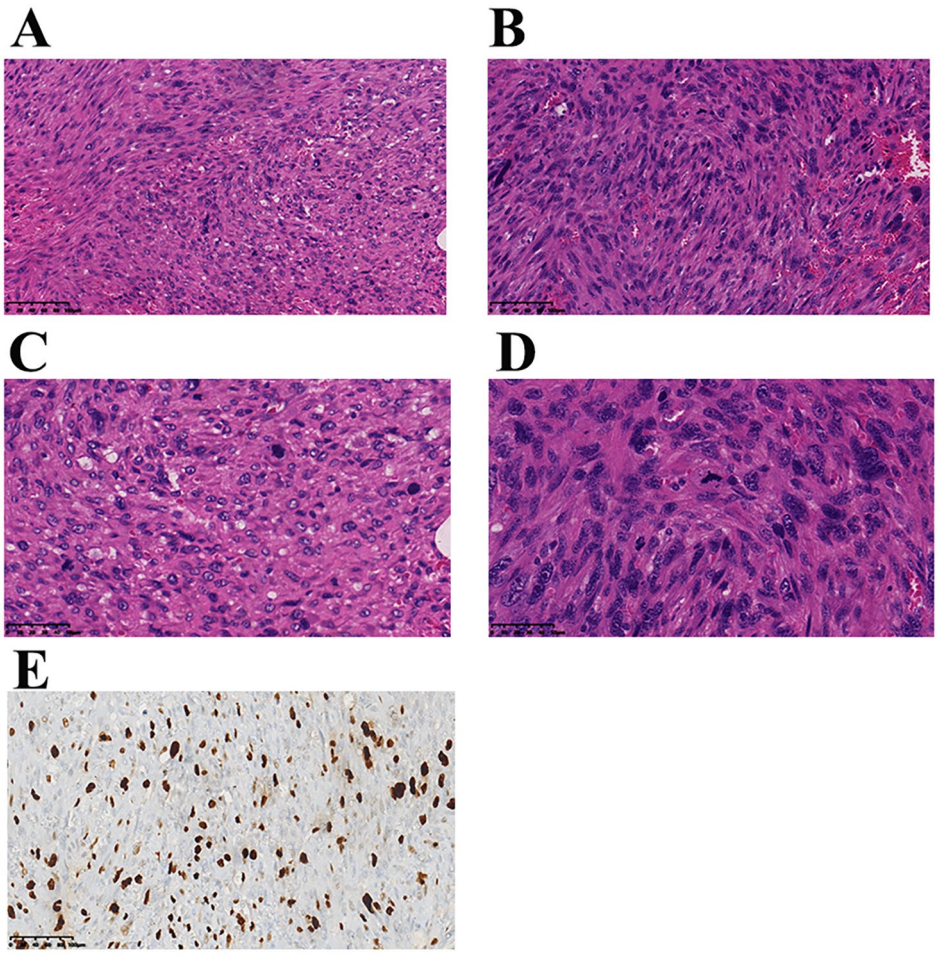

Fig. 2 Morphologic and immunohistochemical findings in Case 1. Fat fusiform or oval neoplastic cells are interspersed with pleomorphic neoplastic cells containing numerous mitotic Fig. (200x **A**, **B**); The cells exhibit a diffuse pattern with abundant and eosinophilic cytoplasm, coarse nuclear chromatin, discernible nucleoli, and a profusion of small vessels (400x **C**, **D**); The Ki-67 index in the hotspot area was approximately 50% (200x **E**)

primary lesion of case 3 (Fig. 4O); all other biomarkers were negative.

DNA-NGS identifies recurrent mutations in TP53

The genomic landscape of UPS was explored through the application of DNA-NGS on the three tumors. For DNA-NGS analysis, a total of 7 variations corresponding to 6 genes including *TP53*, *FANCC*, *STAG2*, *EED*, *SPRY4*, and *RB1* which were all tumor suppressor gene (TSC) were identified in the three samples (Table 1). Two genes among the above with significant abnormalities: *TP53* missense mutation (c.643 A>G (p.S215G)), *TP53* frameshift mutation (c.459del (p. G154Afs*16)), and *RB1* splice mutation (c.2660_2663+16del), predicated to be pathogenic by predicted tools (Table 1). The only recurrent gene (*TP53*) was identified as a potentially druggable gene by the drug–gene interaction database (DGIdb).

Somatic copy number alteration and TMB analysis using DNA-NGS data

The somatic copy number variation (CNV) analysis was conducted on all three samples, revealing CNV gains in two oncogenes, namely *MCL1* and *MYC* in case 2 (Table 1). The respective TMB values were 5.9 mut/Mb, 1.0 mut/Mb, and 3.0 mut/Mb for case 1 to case 3.

RNA-NGS identifies a novel gene fusion *COL3A1-GULP1*

Using two bioinformatic fusion callers and following a series of filtering steps described in the materials and methods, a novel *COL3A1-GULP1* fusion (*COL3A1*: exon23-*GULP1*: exon5) was detected in case 2 (Fig. 5).

Discussion

The occurrence of radiotherapy-induced sarcoma is infrequent presenting a complex and clinically challenging category of tumors. These tumors are highly aggressive and offer very few effective therapeutic options [2, 14]. The reported incidence rates in the literature ranged

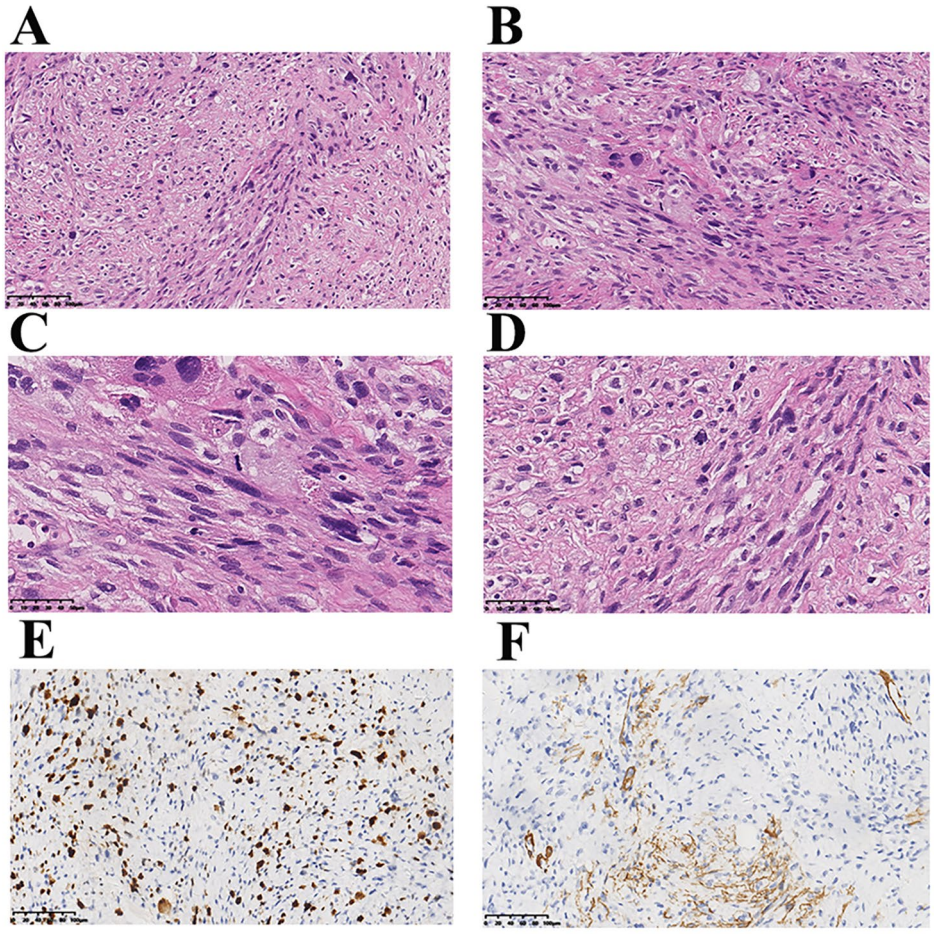

Fig. 3 Morphologic and immunohistochemical findings in Case 2. Case 2' s patient presented with a composition of round, oval, and spindle cells with vacuolar or pale cytoplasm and coarse nuclear chromatin (200x **A**, **B**); pleomorphic tumor cells with briskly mitosis (400x **C**, **D**); High Ki-67 index was about 60% in hotspot area (200x **E**) and SMA was focally positive (200x **F**)

from 0.008 to 0.8% [2, 14]. And, the occurrence of RIS followed by breast cancer was approximately 0.11% among the cohort of 2700 breast cancer patients who received radiotherapy at our institution between 2006 and 2023.

The most frequently reported RIS is angiosarcoma, which distinguishes itself from primary breast angiosarcoma or soft tissue angiosarcoma in terms of clinicopathologic and genomic characterization [1]. To date, no prognostic and genomic studies have conducted a comparative analysis between primary breast UPS and UPS induced by radiotherapy. The present study provides a comprehensive review of radiotherapy-induced UPS based on the available English literature, as summarized in Table 2. The analysis includes key factors such as age of onset, latency period, tumor size, and treatment regimen. Among the 10 cases with available follow-up information, two patients succumbed to the disease within one year, while two patients remained alive despite experiencing multiple relapses. The remaining patients were followed up for a period ranging from 44 months to 174 months without any evidence of recurrence or metastasis. Nevertheless, given its high-grade malignancy and limited therapeutic options, UPS carries an unfavorable prognosis regardless of whether it arises de novo or as a consequence of prior irradiation.

The etiology of radiotherapy-induced sarcoma is associated with double-stranded DNA damage caused by radiation, leading to genomic instability that may result in the development of sarcomas [3, 14, 27]. The risk of radiotherapy-induced sarcoma generally increases with higher radiation doses, exposure during childhood, concurrent chemotherapy, and the presence of genetic disorders such as ataxia-telangiectasia and *BRCA-1* mutation [2]. Molecular investigations of sarcomas induced by radiotherapy commonly reveal inactivation of the p53 pathway [28]. The genomic variants of the three patients exhibited significant dissimilarities, with only shared *TP53* variants identified in patient 1 and patient 2 but at distinct variant sites. The *TP53* gene is frequently mutated in both primary and secondary soft tissue UPS,

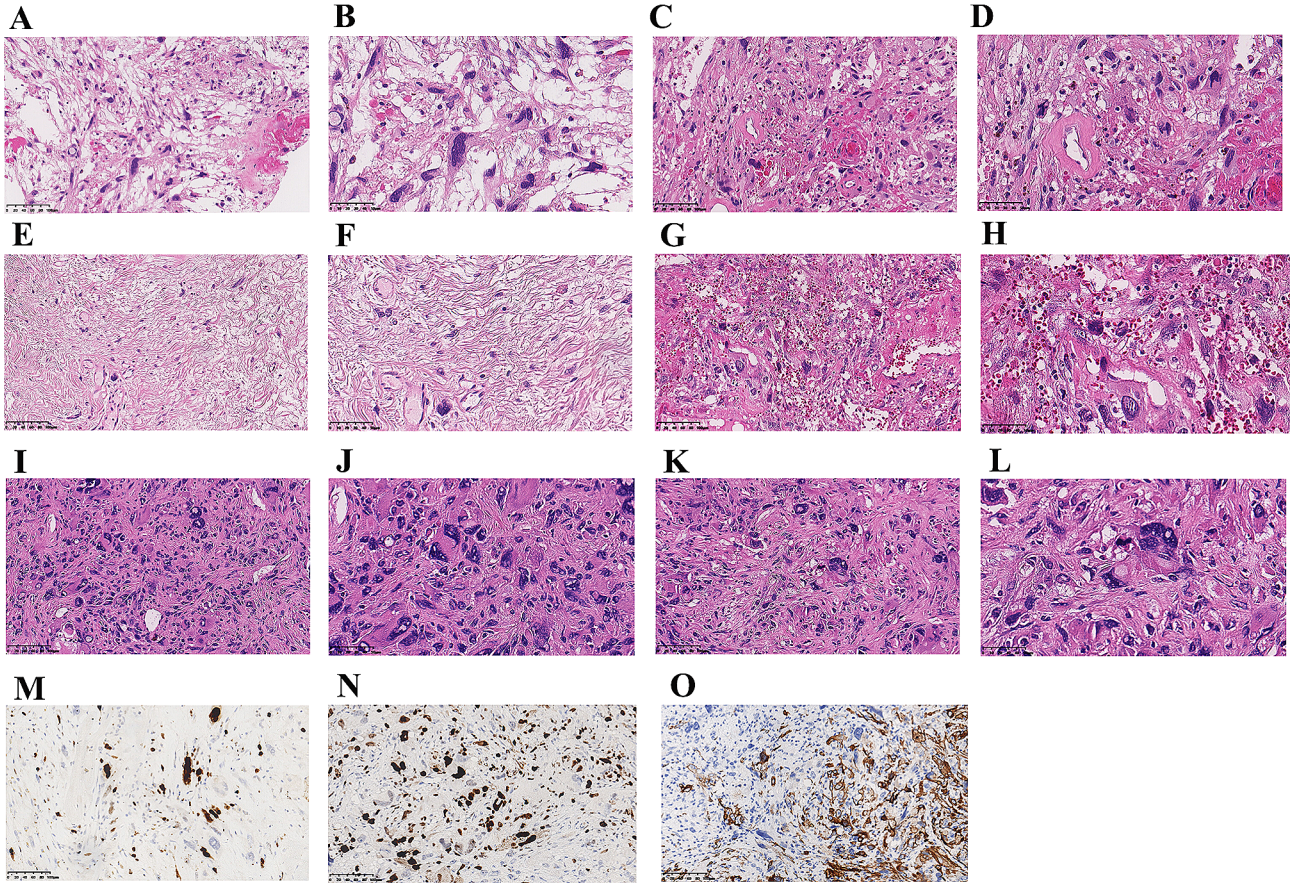

Fig. 4 Morphologic and immunohistochemical findings in Case 3. The tumor in Case 3 exhibited heterogeneity: The core needle biopsy (CNB) specimen exhibited a loosely arranged cellular structure characterized by polymorphic macro-cells and mitosis (200x **A**, **C**, 400x **B**, **D**); The resection showed relatively sparse tumor cells with rough chromatin, interspersed between collagen fibers in some area (200x **E**, 400x **F**); In other area, relatively dense cells that featured prototype oval giant tumor cells with rough chromatin (200x **G**, 400x **H**); The metastatic lesion exhibited a relatively dense arrangement of spindle-shaped and oval cells interspersed with megakaryocytes, and mitotic figures was observed (200x **I**, **K**, 400x **J**, **L**). The Ki-67 index in the primary lesion (200x **M**) was approximately 35%, whereas it exhibited a relatively higher value of around 50% in the metastatic lesion (200x **N**). The primary lesion in case 3 demonstrated focal positivity for SMA (200x **O**), whereas the metastatic lesion exhibited negativity for SMA

with a mutation rate ranging from 13 to 32% [27–31]. Radiation therapy immediately induces DNA damage in cells within the treatment field, which is repaired sequentially, minimizing double-strand breaks and deletions formation [3]. The mutation of the *TP53* gene results in the impairment of its repair function, consequently leading to the development of radiotherapy-induced sarcoma. Besides the radiotherapy-induced UPSs documented in this study, *TP53* is also a prevalent variant observed in other cases of radiotherapy-induced sarcomas [32]. In this study, both *TP53* mutation sites (exon 6 missense mutations c.643 A>G (p. S215G) and exon 5 c.459del (p. G154Afs*16)) are predicted to be pathogenic, resulting in impaired DNA damage repair function. Another pathogenic gene is the retinoblastoma susceptibility gene *RB1*, which is the first molecular-defined tumor suppressor gene and a crucial regulator of the G1/S transition in the cell cycle [33]. *RB1* mutations are present in nearly all familial and sporadic cases of retinoblastoma, and this gene exhibits variable mutation frequencies in various other human cancers [34]. Lesluyes et al. reported *RB1* is a common variant gene in both sporadic and post-radiation sarcomas, which is loss of function in nearly 75% of all such tumors [28]. The *RB1* gene's exon 25 (c.2660_2663+16del) shear mutation may cause the loss of the RB1 protein's ability to inhibit tumor growth, impair transcriptional control, promote unchecked cell proliferation, prevent apoptosis, postpone cell senescence, and contribute to the occurrence and growth of tumors. No other genes typically seen in radiotherapy-induced UPS were discovered in our analysis, in addition to the two genes mentioned above.

Additionally, our cases exhibit amplification of *MCL1* and *MYC*. *MCL1*, a member of the *BCL-2* family with anti-apoptotic properties, hinders mitochondrial outer membrane penetration (*MOMP*) and the release of mitochondrial cytochrome C [35]. The survival of various cell types, including nerve cells, lymphocytes, and

Table 1 Genes for which variants were detected in radiation-induced sarcoma genomes after breast cancer

patient	gene	gene type	coding(c.) nomenclature	RefSeq NM	Type of alteration	franklin	Prediction of functional consequence		
							SIFT.pred	PolyPhen.pred	CADD_phred
1	*TP53*	Tumor suppressor	c.643A > G (p.S215G)	NM_000546.6	Missense mutation	Likely pathogenic	Deleterious	D	Deleterious
	FANCC	Tumor suppressor	c.482T > A (p.L161H)	NM_000136.3	Missense mutation	VUS	Deleterious	D	Deleterious
	STAG2	Tumor suppressor	c.1556G > A (p.S519N)	NM_006603.5	Missense mutation	VUS	Tolerated	B	Deleterious
2	*TP53*	Tumor suppressor	c.459del (p.G154Afs*16)	NM_000546.6	Frameshift mutation	Likely pathogenic	Likely pathogenic	-	Tolerated
	EED	Tumor suppressor	c.190G > A (p.G64R)	NM_003797.5	Missense mutation	VUS	Tolerated	P	Deleterious
	MCL1	oncogene	-	NM_021960.5	Amplify (CNV:8.3)	-	-	-	-
	MYC	oncogene	-	NM_002467.6	Amplify (CNV:9.3)	-	-	-	-
3	*SPRY4*	Tumor suppressor , oncogene	c.89G > A (p.R30Q)	NM_001127496.3	Missense mutation	VUS	Tolerated	D	Deleterious
	RB1	Tumor suppressor	c.643A > G (p.S215G)	NM_000321.3	Shear mutation	Likely pathogenic	-	-	Deleterious

VUS: variant of unknown significance; CNV: copy number variation; D: probably damaging; P: possibly damaging; B: benign;

Fig. 5 Molecular findings. A RNA NGS-based technology revealed the *COL3A1-GULP1* fusion (*COL3A1*: exon23 - *GULP1*: exon5)

myocardial cells, is reliant on the presence of *MCL*[36–38]. Additionally, *MCL1* exhibits a high oncogenic potential and has been found to be amplified in 10.9% of tumor samples across multiple malignant carcinoma subtype [36–38]. Overexpression of the MCL1 protein or amplification of the *MCL1* gene can result in drug resistance or poor prognosis in certain tumors [37–39]. In a study, it was reported that there is co-amplification of *MCL1* and *MYC*, which is associated with poor survival in patients with non-small cell lung cancer [40]. The *MYC* oncogene encodes a transcription factor, MYC, which is believed to trigger selective gene expression amplification in order to promote cell growth and proliferation based on current evidence [40, 41]. *MYC* is a frequently amplified gene in radiotherapy-induced angiosarcomas, accounting for approximately more than 90%, whereas it is infrequent in primary breast angiosarcomas [1]. In pan-cancer copy number analysis, *MYC* was identified as the third most frequently amplified gene [41, 42]. The dysregulation of MYC expression in various transgenic mouse tissues leads to tumorigenesis, thereby demonstrating its transformative activity in vivo and providing support for the notion that *MYC* functions as a human oncogene [43, 44]. The present study identified concurrent amplification of *MYC* and *MCL1* in case 2, suggesting a potential collaborative role of these two genes in promoting tumorigenesis. Significant advancements have been achieved in the development of *MCL-1* inhibitors, several of which have

Table 2 The clinicopathological characteristics of radiation therapy-induced undifferentiated pleomorphic sarcoma (UPS) in literature

Number	Cases	Patient profile	Latent period	Tumor size	Treatment	Follow-up
1	Joshua Kong et al. [4]	75years, F	20 years	2.2 cm	resection, radiotherapy	15months, ANED
2	F. Vera-Sempere et al. [9]	39 years, F	5 years	7.0 cm	resection, chemotherapy	1 year death
3	T.J. Hardy et al. [15]	40 years, F	8 years	5.0 cm	radiotherapy	1 year death
4	Tsuneyoshi M et al. [16]	52 years, F	11 years	0.5 cm	resection	recurrence 5 times, alive
5		55 years, F	5 years	7.0 cm	resection	60 months, ANED
6	B. Meunier et al. [17]	62 years, F	17 years	NA	resection, chemotherapy	96 months, ANED
7	Youlia M. Kirova et al. [18]	70years, F	3.5years	NA	resection, radiotherapy	174 months, ANED
8	Rie Horii et al. [19]	45years, F	4 years	0.8 cm	resection	recurrence 4 times, alive
9	I. Komaei et al. [20]	63years, F	6 years	3.0 cm	resection	NA
10	Naohito Hatta et al. [21]	38years, F	7 years	18.0 cm	NA	NA
11	Luna Kadouri et al. [22]	33years, F	4 years	NA	NA	NA
12	Jae Myoung Noh et al. [23]	70years, F	9 years	8.0 cm	resection	NA
133	Claudio Almeida Quadros et al. [24]	44 years, F	7 years	9.5 cm	resection, chemotherapy	44 months, ANED
14	Pierce SM et al. [25]	NA, F	6 years	NA	NA	died of breast cancer
15	Min Wook Joo et al. [26]	70 years,	33 years	4.0 cm	resection	NA

F: female; UPS: undifferentiated pleomorphic sarcoma (UPS); ANED: alive with no evidence of disease; NA: not available

progressed to clinical trials [45]. The direct targeting of *MYC* for therapeutic purposes has proven challenging due to the absence of a well-established ligand-binding domain [46]. Consequently, attention has shifted towards upstream regulators or *MYC* co-activators as potential targets. Targeting these molecular inhibitors has demonstrated reduced *MYC* transcription and protein levels in leukemia and lymphoma cell lines, exhibiting promising antitumor effects in mouse models of Burkitt lymphoma, acute myeloid leukemia, and multiple myeloma [46, 47]. All these genes hold potential as therapeutic targets for tumors with limited treatment options.

We performed a comprehensive genome-wide analysis of radiotherapy-induced sarcomas and correlated it with their transcriptomic consequences to gain deeper insights into the underlying biology of these tumors. While primary undifferentiated pleomorphic sarcomas (UPS) have been found to harbor multiple fusion genes, such as *CLTC-VMP1*, *FARP1-STK24*, and *MED12-PRDM10*, no fusion gene has been reported for radiation-induced UPS [31, 48, 49]. Our study unveiled a novel *COL3A1-GULP1* fusion gene; however, its functional implications remain yet to be elucidated.

In summary, this study presents a comprehensive analysis of the genetic and transcriptomic alterations landscape in radiotherapy-induced UPS after breast cancer, providing valuable insights into its pathogenesis and expanding our understanding of this tumor. The genomic variability and morphological diversity observed suggest that UPS is highly heterogeneous with a poor prognosis. Genetic testing results reveal potential targeted therapeutic options for this type of tumor. As more cases are accumulated, researchers will gain a better understanding of the genome of these tumors and develop effective treatments for these aggressive malignancies.

Abbreviations

BS	breast sarcoma
RIS	radiotherapy-induced sarcoma
UPS	undifferentiated pleomorphic sarcoma
CNV	copy number variation
TMB	Tumor Mutational Burden
NGS	Next-generation sequencing
IHC	immunohistochemistry

Author contributions

Ting Lei and Qing Li contributed in the writing of the manuscript; Zhiyi Shen, Mengjia Shen, and Lingfang Du prepared the Figs. 1, 2 and 3; Yongqiang Shi, Yan Peng, Zidi Zhou, Wenyue Da, and Xi Chen prepared the Figs. 4 and 5 and the Tables 1 and 2. All authors reviewed and approved the manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent

Informed consent was obtained from all individual participants included in the study.

Competing interests

The authors declare no competing interests.

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