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Review article

Is primary breast melanoma a true pathological entity? The argument against it

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ABSTRACT

Background: Previous studies have reported cases of primary melanoma of the breast parenchyma (PMBP), but the pathogenesis of this disease remains poorly understood. We review the presentation and outcomes of reported cases and provide detailed pathological analysis of four additional cases. Furthermore, we discuss potential theories regarding the pathogenesis of this clinical presentation.

Results: We identified 29 published studies (n = 95 patients) and report four new cases (n = 99). Ninety-one (92 %) patients were female, with a median age of 50 years. Previous skin melanomas were reported by 56 % of patients, with the trunk being the most common location (32.7 %) followed by the upper extremities (20 %). The most common tumor location reported (n = 73) was the right (49 %) upper outer quadrant (56 %). The median time from skin melanoma diagnosis to the presence of a breast mass was 65 months (1–192). Nodal status at presentation was reported in n = 67 (68 %) patients. Of these, positive nodal metastases were seen in 40.3 %, while distant metastatic disease at presentation was reported in 30 % of patients. Surgery was performed in 66 %, being partial mastectomy (PM) the most common procedure in 82 %. Adjuvant therapy was described in 38 patients. The reported (n = 12) median survival was 11.5 (1–70) months.

Conclusion: Melanomas identified in the breast parenchyma are likely the result of nodal or hematogenous spread from previously known or unknown melanomas, and should not be considered as PMBP. Management should be multidisciplinary, including surgical excision aimed at

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obtaining negative margins with lymphadenectomy of clinically positive nodes and neoadjuvant/adjuvant immunotherapy.

Abbreviations

ALND	axillary lymph node dissection
EMA	epithelial membrane antigen
GM CSF	granulocyte-macrophage colony-stimulating factor
HMB-45	human melanoma black-45
HER2	human epidermal growth factor receptor 2
IHC	immunohistochemistry
LUOQ	left upper-outer quadrant
MART-1	melanoma antigen recognized by T cells
MiFT-1	microphthalmia-associated transcription factor-1
MRI	magnetic resonance imaging
MIBT	melanoma in breast tissue
OS	overall survival
PDL-1	programmed death-ligand 1
PET/CT	positron emission tomography/computed tomography
PFS	progression-free survival
PM	partial mastectomy
PMBP	primary melanoma of the breast parenchyma
PR	progesterone receptor
RUOQ	right upper-outer quadrant
S-100	soluble in 100 %

1. Introduction

Melanoma ranks as the fifth most common cancer diagnosis in the United States, with an overall 5-year survival rate of 93.3 % [1]. In approximately 95 % of cases malignant melanoma is localized to the skin [2]. However, there are rare instances in which melanoma can originate from mucous membranes (i.e., mouth, gastrointestinal tract, or ocular structures), or present as metastatic disease with an unknown primary location [2]. While melanoma is typically confined to a specific anatomical site at the time of diagnosis and is primarily managed with surgical intervention [3], it is not uncommon for the disease to metastasize, having a significant impact on the prognosis [4]. Melanoma can spread to various locations, including the skin and subcutaneous tissue, lymph nodes, lungs, liver, brain, and bones.[4] Regional lymph nodes often show the first signs of metastasis, but approximately 25 % of patients develop metastases in distant regions without the lymph node involvement [2]. Malignant melanoma has the ability to metastasize to almost any organ in the body. In patients with distant metastases (Stage IV melanoma), this is the leading cause of mortality, and the historical estimated 5-year survival rate is less than 20 % [5].

The occurrence of melanoma in breast tissue (MIBT) is a rare phenomenon, and while some authors have proposed this melanoma to be a metastatic event, others suggest this to be a primary tumor originating from ectopic melanocytes [6]. These tumors are usually reported as primary melanoma of the breast parenchyma (PMBP). However, the underlying mechanism responsible for this presentation remains unclear. The true incidence of PMMB is currently unknown [7].

The objective of this paper was to investigate the concept of primary melanoma of the breast parenchyma by performing a comprehensive review of published cases and presenting four additional cases. Through in-depth pathological analysis and a discussion challenging the conventional understanding of MIBT, this study aimed to shed light on the pathogenesis of melanomas found in the breast parenchyma.

2. Methods

A MEDLINE/PubMed search from January 1956 through March 2023 was carried out using the terms: breast melanoma, primary breast melanoma, mammary melanoma, metastatic mammary melanoma, primary melanoma of breast parenchyma, in-transit breast/mammary melanoma metastases, and metastatic melanoma to the breast was conducted. We reviewed all papers generated in the search focusing on demographics, clinical presentation, and histopathological features. Melanomas originating from the skin on the breast were excluded. For the case illustration, each patient chart was reviewed thoroughly, including history, imaging, clinical findings, pathology reports, tumor markers, treatment, and discussions held by the tumor board (Fig. 1).

3. Results

Our search of the MEDLINE/PubMed database yielded 32 articles within the last 67 years and of these, 29 articles met our selection criteria [6,8–35], with 95 reported cases published in the literature. In addition to these published cases, we included our own 4 additional cases, bringing the total number of cases included in our analysis to 99 (Table 1).

A Case Presentations:

3.1. Case 1

3.1.1. Clinical presentation

A 60-year-old Peruvian woman presented with a painful, progressively enlarging breast mass in the left upper-outer quadrant (LUOQ) without axillary or supraclavicular lymphadenopathy, which was first noticed 6 years before presenting to the clinic.

3.1.2. Imaging studies

Imaging studies, such as previous mammograms, identified an intramammary node in the tail of Spence correlated with the area of concern (Fig. 2A). Subsequently, a left breast mammogram revealed a BI-RADS 4C, a 3.3 cm hypoechogenic mass with a macro-lobulated margin localized 9 cm from the nipple in the LUOQ (Fig. 2B).

3.1.3. Diagnostic procedures

For diagnosis, an ultrasound-guided core needle biopsy revealed fibro-collagenous tissue with abundant hemosiderin-laden macrophages consistent with an organizing hematoma. Then, excisional biopsy was recommended but the patient did not present for biopsy. Three months later, the size of the lesion had increased to 4.7 cm. At this time, excisional biopsy was performed, being positive for malignant melanoma with a positive lateral margin. Intraoperatively, the mass was noted to be lobulated, adherent to the pectoralis major muscle with feeding blood vessels and surrounded by areas that appeared to be clots likely related to a bleeding necrotic tumor. Immunohistochemical staining was positive for human melanoma black-45 (HMB-45), Melan-A, and soluble in 100 %

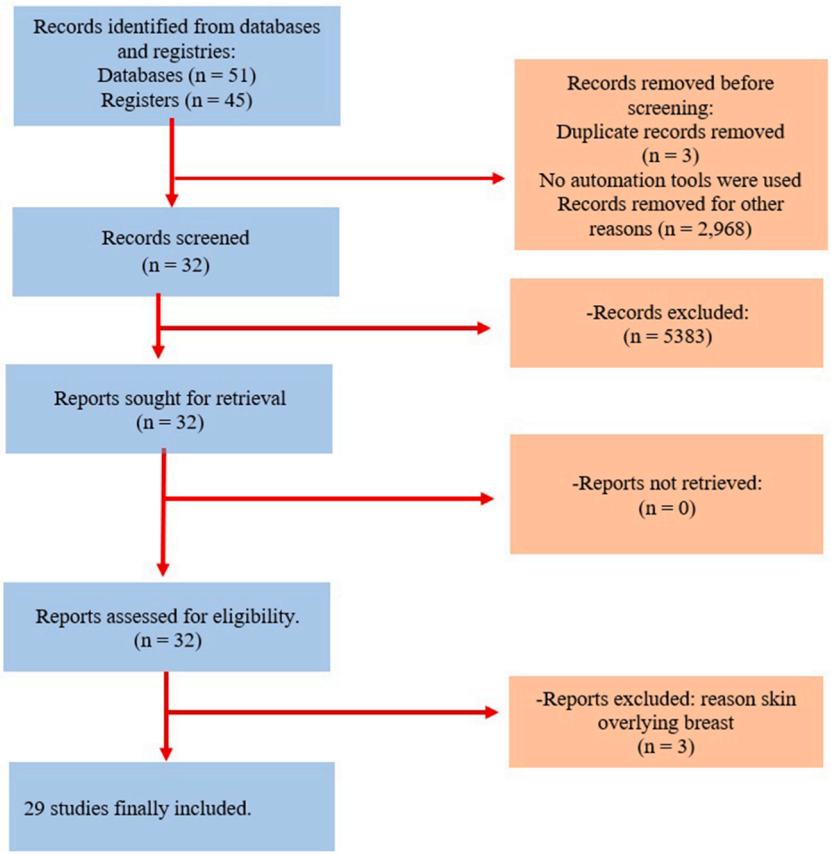

Fig. 1. Review process flowchart.

Table 1
Breast melanoma found in breast parenchyma, cases reported in the literature.

Publication	Author, Year	Cases	Age(y)/ Gender	Anatomical Primary melanoma finding	Time to metastasis (months)	Breast Location/Size (cm)	Lymph Node Involvement	Histology	IHC[11] +ve	IHC[11] -ve	Surgical treatment	Adjuvant Therapy	Follow-up status
1	Bernado et al., 1980 [8]	1	76F	Breast	N/A	Left lower inner: 2.5 cm	Yes**	Meshwork of spindle cells with heavy granular pigmentation	N/A	Not reported	MRM [16]	Mono-chemotherapy (not-specified)	Death at 11 months
2	Vergier et al., 1991 [9]	1	29F	Breast	N/A	Not reported	Not reported	Not reported	Not reported	Not reported	No breast surgery described/no node dissection	Not reported	Does not report condition at LTF [12]
		1	32F	Breast	N/A	Right breast/ 6.5 cm	Not reported	Not reported	Not reported	Not reported	No breast surgery described/1 SLNB[25]	Not reported	Death in 12 months
		1	61F	Breast	N/A	Left breast: 1 cm	Not reported	Not reported	Not reported	Not reported	No breast surgery described/No nodal dissection	Not reported	Death in 5 months
3	Cangiarella et al., 1998 [10]	7	Range 34–71/ 5F and 2M	1 Abdominal wall 1 Eye 1 Right thigh 1 Right arm 2 Unknown	1–60 months	5 Right and 2 Left: 0.8–3 cm.	Not reported	FNA [8]: single cells with eccentric nuclei, prominent nucleoli, intranuclear inclusions of cytoplasm, and dense cytoplasm with small intracytoplasmic vacuolation. One case was amelanotic[a]	Not reported	Not reported	Not described	Not reported	Not reported
4	Kobayashi et al., 2000 [11]	1	47F	Breast	N/A	Right lower: 3 cm	Yes (contralateral) **	FNA [8]: cellular, single population of large-sized discohesive, pleomorphic spindle cells that were arranged singly and in loose fascicles with large, spindled nuclei with coarse, irregularly distributed chromatin and prominent nucleoli. The mitotic rate was high, and there were many individual necrotic cells, but the background was clean. No pigment was observed. No histopathology on breast	Vimentin, HMB-45 [7]	CK [4] S-100 [23]	No breast surgery described	Not reported	Not reported

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Table 1 (*continued*)

Publication	Author, Year	Cases	Age(y)/ Gender	Anatomical Primary melanoma finding	Time to metastasis (months)	Breast Location/Size (cm)	Lymph Node Involvement	Histology	IHC[11] +ve	IHC[11] -ve	Surgical treatment	Adjuvant Therapy	Follow-up status
5	Kim et al., 2003 [12]	1	56F	Breast	N/A	Left upper outer quadrant: 5 cm	No	Pleomorphism with clear cytoplasm, and prominent nucleoli, frequent mitosis but no melanin	HMB-45 [7] S-100 [23]	ER [5] PR [21]	MRM [16]	Chemotherapy	Not reported
6	Artal et al., 2004 [13]	1	30F	Breast	N/A	Right upper outer: 1.2 cm	Yes**	Nuclear atypia, pleomorphic nuclei and prominent nucleoli with some intracytoplasmic inclusions and numerous mitoses, some of them atypical (proliferative marker Ki-67 highly positive), and occasionally lymphoid foci	S-100 [23] HMB-45 [7] MART-1 [14] Vimentin CK [4]	Myoglobin Actin Calretinin EMA [6]	PM [19] and ALND [2]	Not reported	RE[20] in 3 months with RE
7	Loffeld et al., 2004 [14]	8	47-58/ 8F	R Lower leg L ankle L toe Acral Superficial R calf Abdomen Head and neck L scapula	Range 13-178	4Right upper Outer 1 Right medial upper 3 Right Medial lower	Yes (3)	Not reported	Not reported	Not reported	4 p.m. [19] ALND [2]	Not reported	Survival 2–14 months
8	Ravdel et al., 2006 [15]	27	Median 41.4 Median 50 Range (27–70) F	Arm = 8 Trunk = 6 Eye = 3 Head and Neck = 2 Not reported = 2 Unknown = 2 Leg = 4	Median 52.5 Range (1–192)	6 Multiple 5 bilateral (Quadrant not reported) 2 of the multicentric melanomas were bilateral	Yes (3)** but does not specify which patients	Histology diagnosis confirmed in 17 out of 25 patients	S-100 [23] HMB45 [7]	No breakdown	7 p.m. [19] or MRM [16]	20 Chemotherapy and/or radiotherapy (not specified by case)	Median 12.9 (2–37) months survival
9	Vaughan et al., 2007 [16]	6	Range 26-80 Sex not reported	Breast	9–276 Mean 78.2	3 Right 3 Left	Not reported	Not reported	Not reported	Not reported	1 Excision 2 No surgical treatment 1 SM [24] 1 Excision + ALND [2] 1 MRM [16]	Not reported	Survival 5-38
10	Roy et al., 2008 [17]	1	40F	Breast	N/A	Right central: 3 cm	No	Large pleomorphic cells with vesicular nucleus with moderate nuclear membrane irregularity, single large nucleolus,	S-100 [23] HMB-45 [7]	CK [4] EMA [6] SMA [24] ER [5]	SM [24]	None	Alive but no report on disease status LTF [12]

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Table 1 (*continued*)

Publication	Author, Year	Cases	Age(y)/ Gender	Anatomical Primary melanoma finding	Time to metastasis (months)	Breast Location/Size (cm)	Lymph Node Involvement	Histology	IHC[11] +ve	IHC[11] -ve	Surgical treatment	Adjuvant Therapy	Follow-up status
								moderate dense eosinophilic cytoplasm. Amelanotic[a]		PR [21] HER2 [10]			
11	Uludag et al., 2009 [25,36]	1	50M	Breast	N/A	Left lower inner: 0.8 cm	No	Spindle cells located in dermis and subcutaneous tissue and malign tumor infiltration which contained round cells with distinct pleomorphic cytoplasm were identified	S-100 [23]	CD34 SMA [24] CEA [3] HMB-45 [7] CK [4] ER [5]	PM [19]	Not reported	Not reported
12	Samaraee et al., 2012 [19]	1	42F	Breast	N/A	Left upper outer: 2 cm	Yes**	Spindle cells located in dermis and subcutaneous tissue and malign tumor infiltration which contained round cells with distinct pleomorphic cytoplasm	S-100 [23] HMB-45 [7] Melan-A	Not described	PM [19]	Chemotherapy	Not reported
13	Bacchi et al. [20],	20	Range 27–91/ 3M and 17F	17 Breast 1 Toe 1 Abdomen	17 N/A Toe 48m Abdomen unknown interval Choroidal72m	11 Right 5 Left 4 Unknown	Not reported	10 had epithelioid and spindle cells. 10 range highly necrotic neoplasm with palisading cells, vacuolated, lipoblast-like cells, sheets of poorly differentiated cells	All positive for S-100 [23] HMB-457 Melan-A	All negative for CK [4] ER [5] PR [21] HER2 [10] CD45 Desmin	13 p.m. [19] 1 SLNB [25] 1 Radical mastectomy 1 ALND [2]	Not reported	Only 5 had follow-up. 2 alive (no time specified) 2 distant metastases 1 Died from metastasis at 24 months
14	Biswas et al., 2014 [21]	1	32F	Breast	N/A	Left lower inner: 4 cm	Yes**	Abundant clear cytoplasm and large vesicular nucleus with prominent nucleolus. Amelanotic[a]	S-100 [23] HMB-45 [7]	CK [4] EMA [6] Vimentin SMA [24] ER [5] PR [21] HER2 [10]	WLE [26] ALND [2]	Radiation, INF-α2b	NED [17] at 9 months
15	He et al., 2014 [37]	1	26F	Breast	N/A	Left upper inner: 3 cm	Yes**	Round or oval cells with large nuclei and nucleoli and abundant cytoplasm	S-100 [23] HMB-45 [7] Melan-A	CK [4] EMA [6] Vimentin SMA [24] ER [5] PR [21] HER2 [10]	Refused surgery	Refused chemotherapy, immunotherapy, or radiotherapy	Dead at 2 months with widespread metastases
16	Moschetta et al., 2014 [23]	1	39F	Trunk	72	Left breast: 1.4 cm	Yes** (abdominal)	FNA[8]: macroscopically dark and therefore highly suggestive of melanocytic pigmentation	S-100 [23] HMB-45 [7] Melan-A	Not reported	Not reported	Radiation (Brain metastasis) Dabrafenib	Alive but does not report follow-up
17	Vasudevan et al., 2014 [24]	1	50F	Breast	N/A	Left upper outer: 4 cm	Yes**	Moderate amount of eosinophilic cytoplasm	S-100 [23] HMB-45 [7]	N/A	MRM [16]	None	Not reported

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Table 1 (*continued*)

Publication	Author, Year	Cases	Age(y)/ Gender	Anatomical Primary melanoma finding	Time to metastasis (months)	Breast Location/Size (cm)	Lymph Node Involvement	Histology	IHC[11] +ve	IHC[11] -ve	Surgical treatment	Adjuvant Therapy	Follow-up status
								and round pleomorphic nucleus	CK [4] AE1/AE3 [1]				
18	Srikanth et al., 2014 [25]	1	54M	Breast	N/A	Left: 2 cm	Yes**	FNA[8]: highly cellular smears comprising of elongated and spindle shaped tumor cells having prominent nucleoli in a background of melanin pigment	Not done	Not done	MRM [16]	Not reported	Not reported
19	Drueppel et al., 2015 [26]	1	54F	Breast	N/A	Left upper outer: 10 cm	No	Undifferentiated histology.	S100 [23] Melan-A Vimentin	HMB-45 [7] Desmin Actin CD-34 ER [5]	SM [24], SLNB [25]	INF-α	NED [17] at 6 months
20	El-Tani et al., 2016 [27]	1	58 F	Breast	N/A	Right lower quadrant: 2 cm	Yes**	Tumor cells were of medium size with hyperchromatic nuclei and anisokaryosis	S-100 [23]	Melanin-A HMB-45 [7] Keratin 5/6 Actin Desmin Caldesmon Pancytokeratin BRAF	MRM [16]	Ipillumimab	LTF [12] at 8 months
21	Rassouli 2016 [6]	1	50F	Breast	N/A	Right outer: 1.2 cm	No	Irregular cells with abundant amelanotic[a] cytoplasm and prominent nuclei	S-100 [23] HMB-45 [7] Melan-A BRAF V600E	CK [4] ER [5], PR [21] p63	PM [19], SLNB [25]	INF- α2	NED [17] at 1 year
22	Feng et al., 2016 [28]	1	55F	Anorectal	13	Left upper outer: 1.45 cm	No	Consistent finding with a previous anal melanoma but not otherwise specified	Vimentin S-100 [23] Melan-A HMB-45 [7] Pax-5 CD3	CK [4] ER [5] PR [21] Her2 [10] P63 Chromogranin-A GATA-3 [9\	PM [19]	Not reported	Not reported
23	Sathiah et al., 2017 [29]	1	58F	Breast	N/A	Left lower inner 4.5 cm	Yes**	Dyscohesive pattern of tumor cells with heterogeneous	HMB-45 [7]	Mucin CK [4] Vimentin	Not reported	Dacarbazine	Not reported

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Table 1 (*continued*)

Publication	Author, Year	Cases	Age(y)/ Gender	Anatomical Primary melanoma finding	Time to metastasis (months)	Breast Location/Size (cm)	Lymph Node Involvement	Histology	IHC[11] +ve	IHC[11] -ve	Surgical treatment	Adjuvant Therapy	Follow-up status
								morphology. Predominance of signet ring cell morphology along with many binucleated and multinucleated forms. Amelanotic[a]	S-100 [23] Melan-A				
24	Koh et al., 2019 [30],[a]	1	70F	Breast	N/A	Right upper inner: 2.1 cm	No	Polygonal epithelioid cells with eosinophilic cytoplasm and oval eccentric nucleus, no significant pigmentation	S-100 [23] BRAF V600E	CK [4] HMB-45 [7] EMA [6]	PM [19], SLNB [25]	Immune checkpoint inhibitor therapy (unknown)	RE [20], metastasis to left neck, left adrenal gland, left thigh muscle and peritoneum.
		1	30F	Breast	N/A	Left: 4.5 cm	Yes**	Atypical melanocytic proliferation with heavy pigmentation was observed	HMB-45 [7] BRAF S-100 [23]	CK [4]	PM [19], ALND [2]	Immune checkpoint inhibitor therapy (unknown)	Metastasis to Bone and Disclosive Lungs at 8 months
25	Mastoraki et al., 2020 [31]	1	51F	Back	204	Left lower outer quadrant: 5 cm	No	Medium and large epithelioid cells with oval shaped, basophilic nuclei containing intranuclear cytoplasmic inclusions and small eosinophilic cytoplasm	HMB-45 [7] MART-1 [14] Ki-67 80 %	ER [5] PR [21] HER2 [10]	Not described	Nivolumab, Ipilimumab, Vemurafenib	Metastasis to liver and bones
26	Snashall et al., 2020 [32]	1	50F	Breast	N/A	Right, no size described	Yes**	Not reported	S-100 [23] HMB-45 [7]	N/A	PM [19] + SLNB [25]	Immunotherapy but not specified	No RE [20] after 1-year of follow-up
27	Do et al., 2020 [33]	1	58F	Breast	N/A	Left: 10 cm	Yes**	Not reported	S-100 [23] Vimentin MiFT-1 [15]	MART [14] HMB-45 [7] CK [4]	SM [23]	Nivolumab, ipilimumab	Died shortly (no time specified)
28	Sharma et al., 2020 [34]	1	43F	Breast	NA	Left: 2 cm	No	Not reported	S-100 [23] HMB-45 [7] Melan-A	GATA-3 [9] ER [5] PR [21]	No surgery	Immunotherapy Radiation	Not reported

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Table 1 (*continued*)

Publication	Author, Year	Cases	Age(y)/ Gender	Anatomical Primary melanoma finding	Time to metastasis (months)	Breast Location/Size (cm)	Lymph Node Involvement	Histology	IHC[11] +ve	IHC[11] -ve	Surgical treatment	Adjuvant Therapy	Follow-up status
29	Harsten et al., 2021 [35]	1	26F	Breast	N/A	Left upper inner quadrant: 2.2 cm	No	Poorly differentiated malignant tumor	Melan-A	CK [4] ER [5] PR [21] Her2 [10]	No surgery	Pembrolizumab	Not reported
30	Current Case #1	1	60F	Unknown	N/A	Right upper outer: 5.0 cm	Yes**	Atypical, dyscohesive melanocytic cells with nuclear atypia	S-100 [23] HMB-45 [7] Melan-A	CK [4] CD-31 BRAF PDL-1 [19]	PM [19], ALND [2]	Pembrolizumab	RE [20], metastasis to lung, bone. Alive at 70 months after surgery
	Current Case #2	1	65M	Midline chest	144	Left upper outer: 10 cm	Yes**	Sheets of dyscohesive plasmacytoid appearing cells. Nuclei are enlarged, some with prominent nucleoli. Mitotic figures are focally present	S-100 [23]	BRAF PDL-1 [19] FGFR3 GATA-3 [9]	PM [19], ALND [2]	Nivolumab	Metastasis to liver, RE [20] to skin. Death at 35 months after surgery
	Current Case #3	1	46F	Upper chest	23	Left upper quadrants and nipple areolar complex: 3 cm	Yes**	Epithelioid/plasmacytoid cells with abundant eosinophilic cytoplasm, and multipolar mitoses in center	S-100 [23] BRAF SOX-10 Melan-A	PDL-1 [18]	PM [19] ALND [2]	BRAF/MEK inhibitors	RE in 3 months Metastasis to lung and regional nodes. Alive at 65 months after surgery
	Current Case #4	1	41F	Right scapula	155	Left upper outer: 1.4 cm	No	Epithelioid and heavily pigmented. Lymphovascular invasion is identified	Melan-A Sox 10 PDL-1 [18] S100 [23]	BRAF KIT MEK-1 [13]	PM [19]	Nivolumab and ipilimumab offered but did not received treatment	Metastasis to left breast, lung, thoracic nodal, liver, bone, and soft tissue at diagnosis. Death at 6 months after surgery

[1]AR1/AE3 = Pancytokeratin AE1/AE3; [2]ALND = Axillary lymph node dissection; [3]CEA = Carcinomebrionary antigen; [4]CK = Cytokeratin; [5]ER= Estrogen receptor; [6]EMA = Epithelial membrane antigen; [7]HMB-45 = Human Melanoma Black-45; [8]FNA = fine needle aspiration; [9]GATA-3 = Guanin-Adenine-Thymine-Adenosine-3; [10]HER2 = human epidermal growth factor receptor 2; [11]IHC = Immunohistochemistry; [12]LTF = Lost to follow up; [13]MEK-1 = Mitogen-Activated Protein Kinase-1; [14]MART-1 = melanoma antigen recognized by T cells; [15]MiFT-1 = microphthalmia-associated transcription factor-1; [16]MRM = modified radical mastectomy; [17]NED = no evidence of disease; [18]PDL-1 = Programmed death-ligand 1; [19]PM = Partial; [20]RE = Recurrence; [21]PR = Progesterone receptor; [22]S-100 = Soluble in 100 % %; [23]SM = simple mastectomy; [24]SMA = Smooth muscle antigen; [25]SLNB = Sentinel lymph node biopsy; [26]WLE = Wide local excision.

[a] Amelanotic Melanoma (n = 5).

(S-100) and negative for keratin and CD31. Mutational analysis revealed mutations in TP53 and p.C227Y, and negative *ESWR1* gene rearrangement. The mass was initially reported as PMBP; however, upon re-evaluation of previous imaging, a preexisting intramammary node was identified. Pathology examination of the excised specimen confirmed the presence of a lymph node capsule, and the intramammary node was completely replaced by metastatic malignant melanoma. (Fig. 2C).

Further examination and investigation was conducted for completion of diagnosis. A complete skin, mucosal, ear, and eye examination revealed no suspicious lesions of skin cancer. Brain magnetic resonance imaging (MRI) revealed no evidence of metastasis. Positron emission tomography/computed tomography (PET/CT) showed post-operative changes in the left chest region with multifocal hyper-metabolic areas of increased uptake in the left outer chest area, secondary to recent surgery (Fig. 2D). Additionally, a likely reactive right cervical level 2 lymphadenopathy was noted Core needle biopsy of this node showed reactive follicular hyperplasia but no evidence of metastasis by melanoma or lymphoma. Tumor staging was melanoma of unknown primary location TxN3bM0 (Stage IIIC).

3.1.4. Treatment modalities and outcomes

Due to lost to follow up, patient wider resection to clear margins was not carried out. Hence, the treatment at this time was only surgical resection. An 18F-FDG PET/CT performed at the 3-month follow-up showed an increase in size and avidity of the left chest region, with small foci of low uptake in the LUOQ. The patient then underwent complete resection of the tumor with negative margins. However, one month later, additional nodules were presented in the tail of Spence. Physical examination revealed a small post-operative seroma and a new 1 × 1 cm soft tissue mass along the LUOQ. A restaging PET/CT scan showed the development of a cluster of enlarged lymph nodes, measuring 2.5 × 3.9 cm in the LUOQ of the breast (Fig. 2D). The patient underwent surgical resection for locoregional control in preparation for adjuvant immunotherapy treatment.

Intraoperatively, the tumor showed invasion of the pectoralis major muscle, and the adjacent nodes displayed gross disease. The tumor was resected with wide negative margins and left axillary lymph node dissection (ALND) was performed. Pathological examination revealed metastatic melanoma in 9/24 nodes. Residual tumor masses in the tail of Spence nodes were deemed to represent satellitosis and metastases to intramammary nodes. Tumor mutation studies were negative for BRAF, PD1, FGFR3, KRAS, and KIT.

Since progression of disease was noted, the patient underwent adjuvant nivolumab immunotherapy for a year and a half. Later, follow-up PET/CT scans showed resolution of the metastases, and the patient remained stable without evidence of recurrence. The patient was alive without disease at 70 months of follow-up after surgical treatment.

3.2. Case 2

3.2.1. Clinical presentation

A 65-year-old Swedish man presented with a two-month history of a progressively growing right breast mass. Twelve years earlier, the patient was previously diagnosed with cutaneous melanoma of the right chest and was treated with wide surgical excision. On physical examination, a 3 × 3 cm soft, non-tender mass localized in the right upper-outer quadrant (RUOQ) of the breast, 9 cm from the nipple, with no associated palpable lymphadenopathy, and gynecomastia was not observed.

3.2.2. Diagnostic procedures

Diagnostic mammography showed atypical distribution of glandular tissue in the RUOQ of the breast, assessed as BI-RADS 5 (Fig. 3A–B). Ultrasound examination revealed an irregular and heterogeneous solid mass in the RUOQ. Biopsy of the mass demonstrated a poorly differentiated invasive ductal carcinoma, Nottingham grade 3, with triple-negative receptor status. The tumor was E-cadherin positive, which initially supported the diagnosis of invasive ductal carcinoma (Fig. 3C). However, upon further investigation, and considering the patient's history of malignant melanoma and the immunohistochemistry (IHC) results demonstrating the tumor was positive for S100 and negative GATA3 staining, the diagnosis was amended to amelanotic melanoma, with some new distinct molecular features with respect to his previous melanoma diagnosis.

An 18-FDG PET/CT scan demonstrated a 4.6 × 3.8 cm hypermetabolic mass in the right breast abutting the pectoralis muscles with an adjacent 1 cm hypermetabolic lymph node. (Fig. 3D). Additionally, a 1.6 × 1.3 cm hypermetabolic mass was also noted in segment two of the liver.

3.2.3. Treatment modalities

The patient underwent surgical excision of the right breast mass requiring partial excision of the pectoralis muscles due to tumor adherence, along with concurrent ALND. Pathology results revealed a 5 × 4 cm mass identified as melanoma, with 30 % necrosis. Two of the 15 resected nodes were positive for metastatic melanoma. A small nodule from the subcutaneous adipose tissue was completely derived from melanoma cells, suggestive of satellitosis. The patient was diagnosed with Stage IV (T4N3M1c) melanoma. Genetic studies were negative for mutations in BRAF, PD1, FGFR3, KRAS, and KIT. The patient started four cycles of adjuvant immunotherapy with pembrolizumab.

3.2.4. Outcomes

The patient was followed for a total of 39 months, showing disease progression, and undergoing multiple rounds of chemotherapy and additional radiation therapy. Unfortunately, the patient died 35 months after surgery.

3.3. Case 3

3.3.1. Clinical presentation

A 46-year-old Venezuelan woman with a family history of melanoma in two aunts presented with a dark irregular lesion on her left chest in 2015. The lesion was biopsied by her dermatologist in Venezuela, but the specimen was not sent to pathology. The biopsied primary site never healed, and in late 2017, the lesion recurred along with a new mass in her left axilla.

3.3.2. Diagnostic procedures

Wide excision of the recurrent chest lesion was performed along with left ALND, demonstrating metastatic melanoma in 4 of 21 lymph nodes. The depth of melanoma was not available.

3.3.3. Treatment modalities

Only surgical resection was performed at the beginning. A year later the patient moved to the United States, where she received adjuvant treatment with a total of 11 doses of nivolumab.

3.3.4. Outcomes

Eight months later, she returned to our institution with disease recurrence showing three new subdermal nodules beneath the left nipple-areolar complex, along with a nodule at 9 o'clock in the left breast, 2 cm from the areola. Diagnostic breast mammogram and ultrasound demonstrated a 1 x 0.4 × 1 cm superficial nonvascular complex nodule with adjacent duct ectasia at 6 o'clock retro-areolar (Fig. 4A–B). A punch biopsy of the left areola demonstrated melanoma recurrence with in-transit disease (Fig. 4C). MRI demonstrated additional retro-areolar nodular lesions at 6 and 12 o'clock. Morphologically abnormal and enlarged left internal mammary artery lymph nodes measuring up to 1.8 cm in the left fourth intercostal space, with suspicion of nodal metastasis were observed. In addition, enhancing masses in the lungs were described, with the largest mass at the left lung base measuring up to 1.9 cm and with a 1.3 cm enhancing lesion in the right manubrium. A diagnostic brain MRI was negative for brain metastases. An 18-FDG PET/CT study showed worsening of the metastatic disease in the lung, internal mammary nodes, and sternum with bilateral new perihilar lymphadenopathy with abnormal FDG-uptake, and an FDG-avid 0.8 cm inguinal lymph node Stage TxN3M1.

3.3.5. Treatment of disease recurrence

The patient underwent a partial left mastectomy with nipple areolar resection. The final pathological result of the left nipple showed recurrent melanoma, without epidermal component, favoring dermal metastasis with cells demonstrating a plasmacytoid appearance with abundant eosinophilic cytoplasm and irregular nuclei, positive for SOX-10. There was lymphovascular invasion with five out of seven retro-areolar intramammary lymph nodes positive for metastatic melanoma, and negative for extra-nodal extension. These latter nodes were not in continuity with the skin lesion (Fig. 4D). The IHC results were positive for BRAF, S-100, Melan-A, and SOX-10, and negative for PD1. Brain MRI remained negative for metastases. Next-generation sequencing revealed a BRAFV600E mutation; as such, the patient was treated with a post-surgical combination BRAF/MEK inhibitors: encorafenib plus binimetinib, showing resolution of internal mammary, bone and pulmonary metastases without disease recurrence after treatment at 65 months of follow-up.

3.4. Case 4

3.4.1. Clinical presentation

A 40-year-old white American female with a 12-year history of right scapular T1bN0M0 (as per the American Joint Committee on Cancer 8th edition), malignant melanoma, 0.96 mm Breslow depth thickness superficial spreading type. The patient underwent wide local excision with local advancement flap closure and had yearly dermatological follow-ups without evidence of local recurrence.

3.4.2. Diagnostic procedures

During her first routine screening mammogram showing a very dense breast, ultrasound was performed showing a 1.4 cm well-circumscribed oval hypoechogenic mass in the left breast with peripheral and internal vascularity (BIRADS 4 classification) in the left axillary tail. A complete physical examination did not demonstrate any suspicious skin lesion, although in the left breast at the 2 o'clock position 6 cm from the nipple, a nodular mass of 1 cm × 1.5 cm was palpated and correlated with the lesion seen in the ultrasound. These imaging findings prompted a core needle biopsy which demonstrated a malignant melanoma. During work-up, an 18-FDG PET/CT showed widespread hypermetabolic disease in addition to the left breast mass, involving the subcarinal and left perihilar lymph nodes, sternum, ribs, spine, and iliac bones, bilateral proximal femoral bone and bilobar lung metastases (Fig. 5A–B). Brain MRI showed at least 11 nodular foci of intra-axial metastatic disease. An abdominopelvic contrast-enhanced tomography confirmed multiple small hypodense lesions in the liver and widespread lytic lesions in the axial and appendicular skeleton compatible with bone metastases.

3.4.3. Treatment modalities and outcomes

Management of the patient was discussed by the cutaneous oncology multidisciplinary tumor board and PM (metastasectomy) was recommended to evaluate the tumor for next generation gene sequencing and BRAF mutation. The pathological results demonstrated malignant melanoma, epithelioid and heavily pigmented, with lymph vascular invasion and tumor in lymphatic spaces (Fig. 5C–D),

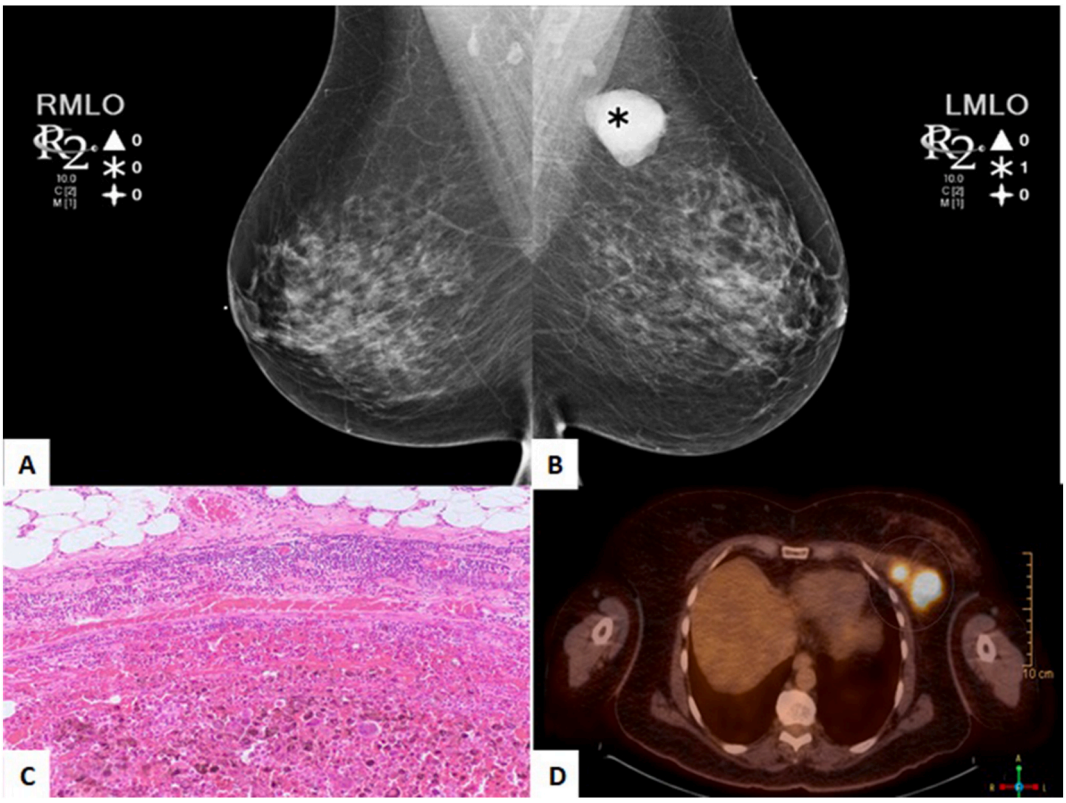

Fig. 2. (Case 1): **A-B.** Initial mammogram findings demonstrate a 3.3 cm round high-density mass with a macro-lobulated margin in the posterior left breast at 1 o'clock depth (marked by an asterisk). No other dominant masses, regions of architectural distortion, or suspicious clusters of microcalcifications are seen. **C.** Interval development of a cluster of enlarged left axillary and left chest wall lymph nodes, the largest of which measures 2.5 × 3.9 cm with abnormal FDG uptake, SUV 11.3. **D.** Histologic section of metastatic malignant melanoma in the lymph node showing large, epithelioid tumor cells with enlarged nuclei, prominent nucleoli and abundant and pigmented eosinophilic cytoplasm. Hematoxylin and eosin (H&E) x100.

positive for Melan-A, Sox 10 and PD1 and focally positive for S100, BRAF, KIT and MEK1 negative. The patient was scheduled to receive nivolumab + ipilimumab treatment at an outside institution. Unfortunately, she died 5 months after the initial diagnosis of metastatic Stage IV melanoma.

B Descriptive variables

3.4.4. Demographics

Of the total number of patients, 91 (92 %) were females, while only 8 (8 %) were males, resulting in a female-to-male ratio of 11:1. Patient age was provided in 72 of the cases, with a median age of 50 years and mean of 49 years. The age range for all patients was 24–84 years (Table 2).

3.4.5. Primary cutaneous melanoma

The presence of primary cutaneous melanoma was reported in 55 (56 %) patients, 5 (5 %) being new diagnoses and 50 (51 %) having a previous history of skin melanoma. The anatomical location of the primary melanoma was reported in 55 patients (56 %). The trunk was the most common location in 18 (33 %), followed by the upper extremity in 1 (20 %), head and neck in 9 (16.4 %), a lower extremity in 11 (20 %), anal in 1 (2 %), and 5 (9 %) were reported as melanoma of unknown primary location, while in 43 (43.4 %) patients, no description was provided regarding previous or current skin melanoma at the time of the diagnosis of breast melanoma. The histological subtype of primary skin melanoma was described only in 7 cases, and of these, 5 (5.1 %) were amelanotic, 1 (1 %) was spitzoid, and 1 (1 %) was mucosa. Twenty-four studies accounting for 79 (80 %) cases provided a very heterogenous histopathological description of the cellularity of the tumor found in the breast (Table 2).

3.4.6. Melanoma breast tumors

Size-specific breast tumors were reported in only 35 patients (36 %), with a mean size of 3.82 cm and median of 3 cm (range 0.8–10 cm). Regarding tumor laterality in the breast, this variable was reported in 73 (74 %) of patients, being the right breast (n = 36, 49.3 %)

slightly more common than the left (n = 32, 43.9 %), and with a bilateral presentation in 5 (7 %) patients. The specific tumor location in the breast parenchyma was heterogeneously reported in 43 (43.4 %) patients. To provide more consistent reporting, we grouped the locations as follows: upper outer quadrant n = 22 (56 %), medial location n = 9 (20.9 %), multifocal n = 8 (18.5 %), lower outer quadrant n = 3 (6.8 %) and central n = 1 (2.3 %) (Table 2).

3.4.7. Immunohistochemistry and biomarkers

Seventy-three (73.7 %) tumors underwent IHC testing. The most common positive stains included: S-100 42 (42.4 %), HMB-45 37 (37.4 %), melanin-A 31 (31.3 %), SOX-10 3 (3 %), vimentin 2 (2 %), MART-1 2 (2 %), actin 1 (0.9 %. Negative stains included: 31 (31.3 %) human epidermal growth factor receptor 2, 28 (28.2 %) estrogen receptor and progesterone receptor (PR), 25 (25.2 %) epithelial membrane antigen (EMA), 6 (6 %) actin, 4(4 %)HMB-45, 3 (3 %) myoglobin, 3 (3 %)vimentin, 1 (1 %) chromogranin, 1 (1 %) synaptophysin, and 1 (1 %) Melan-A. Tumor expression tests showed: BRAF = 7 (7 %), KRAS = 1 (1 %), programmed death-ligand 1 (PDL-1) = 2 (2 %), CD34 = 1(1 %), CD35 = 1(1 %), and p63 = 23 (23.2 %) (Table 1).

3.4.8. Clinical presentation

Nodal status at presentation was reported in 67 (68 %) patients. Positive nodal metastases were seen in 27 (40.3 %) and negative in 40 (59.7 %) of patients and was not described in the remaining 32 (32.3 %) patients.

Distant metastatic disease at presentation was reported in 12 patients. The reported sites of disease were the liver (n = 8), bones (n = 6), brain (n = 3), adrenal glands (n = 2), muscle (n = 2), internal mammary lymph nodes (n = 1), and ilioinguinal (n = 1). The median time from primary melanoma diagnosis to the diagnosis of a breast mass confirming melanoma was 65 (range 1–192) months. In addition, metachronous distant metastatic disease was also reported in 18 % of patients, occurring between 1 and 48 months after the diagnosis of breast melanoma. Of these, 8 patients developed multiple organ metastases. The most common sites of disease were brain (n = 7), lung (n = 4), liver (n = 3), bones (n = 3), subcutaneous tissue (n = 2), adrenal (n = 1), and peritoneal metastasis (n = 1).

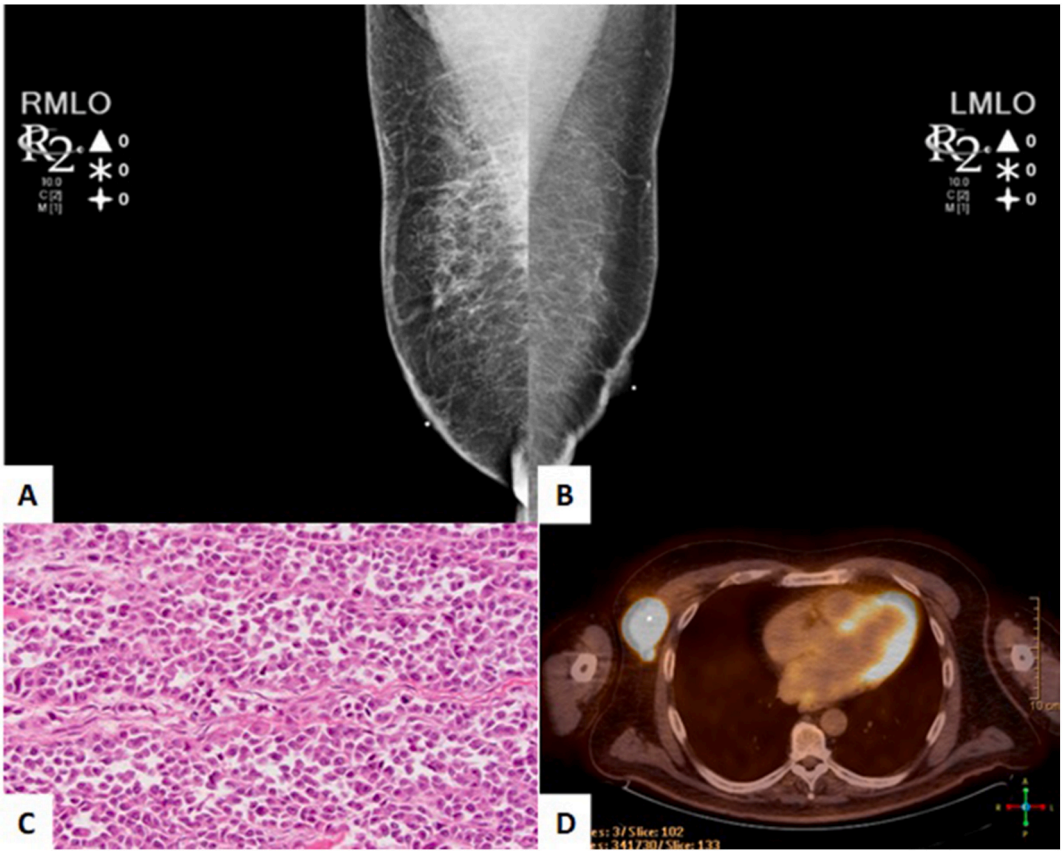

Fig. 3. (Case 2): **A** and **B** Initial mammogram findings demonstrate glandular tissue of the right breast without the typical distribution of gynecomastia. (There is very sparse parenchyma in the subareolar area with the majority toward the upper outer quadrant). Fatty tissue is detected in the left breast. There are no suspicious masses or calcifications. No skin thickening or nipple retraction. **C.** Histologic section of metastatic malignant melanoma in the lymph node showing large, epithelioid tumor cells with enlarged nuclei, prominent nucleoli, and abundant and pigmented eosinophilic cytoplasm. Hematoxylin and eosin (H&E) x100. **D.** PET/CT scan demonstrates 4.6 × 3.8 cm hypermetabolic mass in the right breast, SUV 47.5. The mass is inseparable from the inferior margin of the minor pectoralis muscle and abuts the major muscle. There is adjacent fat stranding. Immediately lateral to the right breast mass there is a 1 cm hypermetabolic lymph node, SUV 19.9.

3.4.9. Surgical intervention

Surgical treatment was reported in 65 (66 %) patients. Various types of breast surgery and axillary surgery were performed. Breast surgery was performed in 44 (44 %) patients. Of these, the vast majority (36; 81.8 %) received breast-conserving surgery, reported as PM, excision, or wide excision. Modified radical mastectomy/extended mastectomies and simple mastectomies were reported in 8 (8 %) patients. Axillary intervention was performed in 21 (21 %) patients, with complete lymph node dissection in 17 patients, and sentinel lymph node biopsy in 4 patients.

3.4.10. Adjuvant therapy

Administration of adjuvant therapy was reported in 38 (38 %) patients. However, in the majority of cases (n = 21), the type of adjuvant therapy was not specified. Of the patients in whom the therapy was specified, 15 patients received immunotherapy (4 were given interferon-alpha, 4 pembrolizumab, 4 nivolumab and/or ipilimumab, and 3 BRAF and/or MEK inhibitors), 4 patients received cytotoxic chemotherapy, and 2 patients radiation therapy. Of all the patients, 2 received combined radio-immunotherapy treatment and 2 received chemotherapy followed by immunotherapy.

3.4.11. Follow-up

Follow-up was described in only 21 patients with a median follow-up of 12 (range 1.5–70) months. Recurrence and survival were reported in a much smaller number of patients. Recurrence of primary melanoma was reported in 7 patients with a mean time to recurrence of 52.25 months. Survival was reported in only 12 patients, with a median survival of 11.5 (range 1–70) months from the time of breast tumor diagnosis.

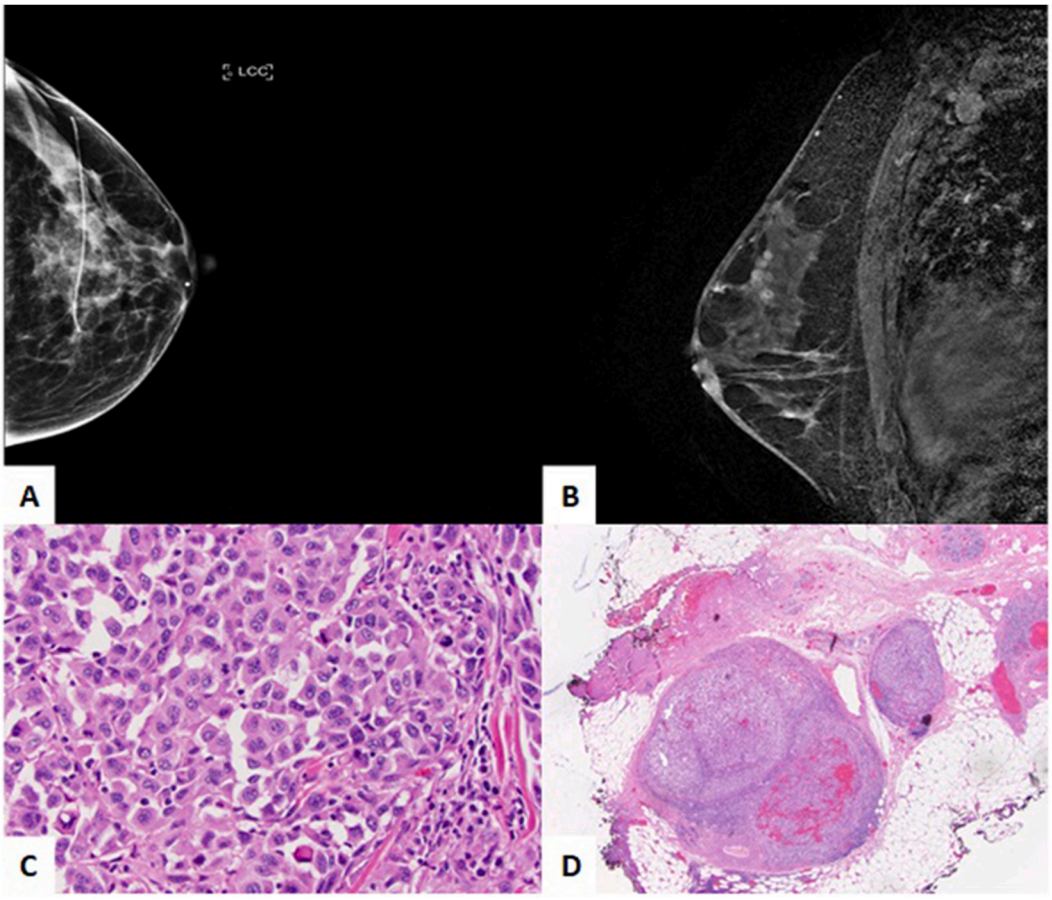

Fig. 4. (Case 3): **A.** Diagnostic mammogram demonstrating a 1 x 0.4 × 1 cm retro-areolar superficial nonvascular complex nodule at 6 o'clock with adjacent duct ectasia. **B**. Diagnostic MRI shows metastatic nodules at 12 o'clock extending into the central breast. **C.** High power view of the melanoma in the breast. The cells are epithelioid/plasmacytoid with abundant eosinophilic cytoplasm and irregular nuclei, high N:C ratio and mitotic figures. (400x). **D.** Several lymph nodes with melanoma metastases, demonstrate a clear capsule and a rim of lymphocytes. Normal breast parenchyma can be seen in the upper right corner. (40x).

4. Discussion

To date, melanoma of the breast remains a rare entity, with only 99 cases including our current patients being documented over almost seven decades. To our knowledge, this is the largest most exhaustive review published in the literature to date. Some authors have proposed three categories to classify melanoma presenting in the breast: primary cutaneous melanoma, PMBP, and metastatic melanoma to breast [38]. The first category refers to melanomas originating from the skin, including the chest and breast area, accounting for about 5 % of all melanoma cases. However, the true incidence of melanomas found in the breast parenchyma is currently unknown, due to the scarce reporting of these cases [7].

MIBT remains a subject of controversy and is often disregarded as a true entity. A review of 6691 cases of non-cutaneous melanomas diagnosed in the United States, reported that 4885 cases were derived from ocular structures and the remaining 1806 cases from mucosal membranes. Notably, no cases of PMBP were reported in that study [39]. It has been suggested that the occurrence of melanoma metastases to the breast may represent the first sign of melanoma recurrence in up to 40 % of cases [39]. Furthermore, breast metastases in malignant melanoma have been associated with shorter survival [9].

In this review of all the currently reported cases, we looked at the clinical presentation of these particular breast tumors. It appears they have a higher tendency to form in the upper outer quadrants of the breast in women in their fifth decade of life. We hypothesize this could be related to the rich lymphatic network and drainage in this area. Only 7 previous cases of males have been reported in addition to our patient. Breast laterality was described in two third of patients, showing no predilection for either breast. In one of the previous series by Bacchi et al. [20] including 20 cases, laterality was only reported in some of the patients. Most patients (82 %) presented with sizeable masses of more than 2 cm at the time of diagnosis.

However, it is of note that more than half (56 %) of the patients in the present review reported the presence of a previous or concomitant malignant cutaneous melanoma, with a wide time frame to the detection of the melanoma mass in the breast parenchyma, ranging from 1 month to 16 years. Regarding our four cases added to his review, one was considered to be a metastatic melanoma of unknown primary, while the other three received previous complete surgical excision of the primary cutaneous melanoma. All our patients presented later recurrences in the breast.

Among the primary locations reported, the trunk and upper extremity were the most common in up to 52 % of cases, with both areas known to drain to the axillary lymph nodes and in-transit nodes in the chest. Regarding our four cases added to this review, one was confirmed to be an intramammary node completely replaced by metastatic melanoma of unknown primary origin, while the other three received previous complete surgical excision of the primary cutaneous melanoma, and all presented as later recurrences in the breast.

Our results are consistent with previous case series, indicating trunk and arm locations being reported as the most common site of primary tumors metastasizing to the breast [9,10,14,15,18,23,31] and usually presented in the outer quadrants [10,12–14,19,21,28,30,34,35].

The histological subtype was mentioned only in a very small number of patients, and thus, the most common primary subtype could

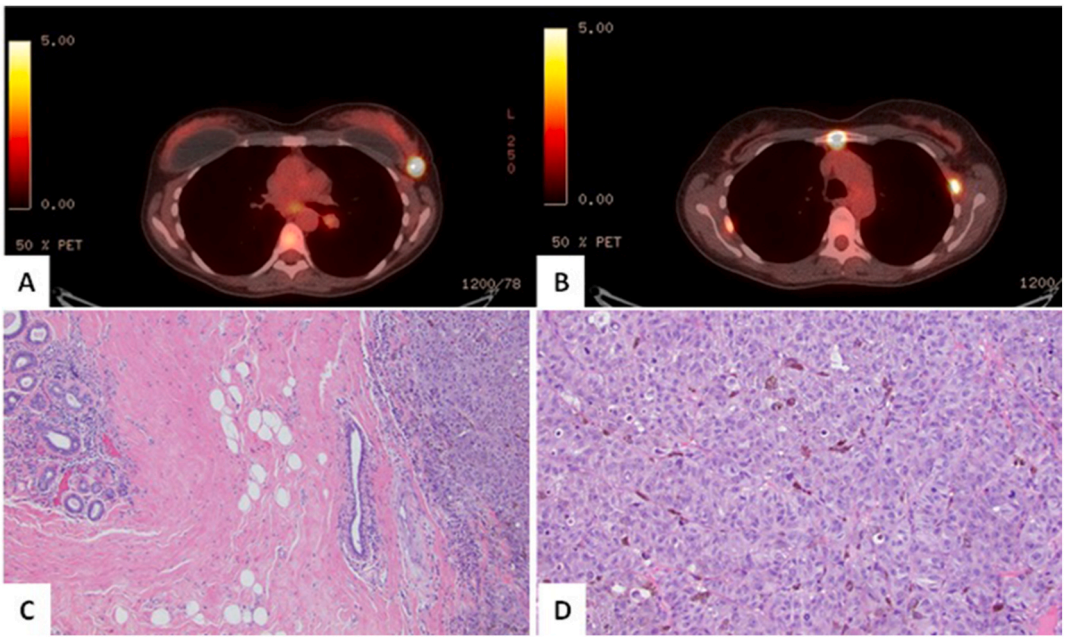

Fig. 5. (Case 4): **A** and **B**. PET/CT scan demonstrating left breast, lung, thoracic nodal, bone, and soft tissue metastases. **C**. Portion of breast parenchyma (left) with fibrous stroma. A well-circumscribed nodule of melanoma is present on the right. (100 X) **D.** Higher power shows the tumor to be composed of epithelioid cells with amphophilic cytoplasm and enlarged ovoid nuclei with prominent nucleoli (400 X).

not be ascertained, as we were limited by heterogeneous reporting of clinical and pathological descriptions with overlapping of some of descriptions.

At least 40 % of the patients in whom the nodal status was reported, presented with clinically positive nodal involvement and 30 % of cases reported the presence of positive distant organ metastases, either as synchronous or metachronous with the breast mass, and 3 % reported a negative workup for distant disease. However, information on nodal status and distant metastatic disease was missing in 33 % and 66 % of patients, respectively, and therefore, the true incidence of nodal and distant metastatis remains unknown and could potentially be higher.

Since the clinical presentation of melanotic tumors in the breast may mimic breast cancer by physical examination and breast imaging. It is important to establish an accurate diagnosis for adequate metastatic workup and improve outcomes. Hence, pathological analysis is crucial to establish the diagnosis to distinguish this tumor from other breast malignancies. The diagnostic procedure preferred is core needle biopsy over fine needle aspiration, as this technique offers the advantage of providing tissue for IHC analysis. The most common immunohistochemical markers used for the diagnosis of melanoma include S-100 protein, Melan-A, and HMB-45 [40,41]. All the above-mentioned cases demonstrated positivity for S-100. Although the S-100 protein, a calcium-binding protein, has a high sensitivity for melanoma (97–100 %), its specificity is only 75–87 % [42]. In fact, S-100 has been reported to be positive in

Table 2
Characteristics of the patients included in the review.

Characteristics	N (%)	Variable	Patients
Sex	99 (100 %)	Male	8 (8 %)
		Female	91 (92 %)
		Not described	0 (0 %)
Age	99 (100 %)	Range 20–84 years	
	72 (72.7 %)	Median 50 years	
		Mean 49 years	
Location of previous skin melanoma	55(55.6 %)	Trunk	18 (32.7 %)
		Upper Extremity	11 (20 %)
		Head and Neck	9 (16.4 %
		Lower extremity	11 (20 %)
		Anal	1(1.8 %)
		Unknown	5 (9.1 %)
	99 (100 %)	No description provided	43 (43.4 %)
Presentation	67 (67.6 %)	Node positive	27 (40.3 %
		Node negative	40 (59.7 %)
	99(100 %)	Do not describe nodal status	32 (32.3 %)
		Distant disease at presentation	12 (12.1 %)
		Previous skin melanoma	55 (55 %)
	55 (55 %)	Median time from skin to breast metastasis 65 months	
	99(100 %)	Developed metastasis after diagnosis	18 (18.1 %)
Location	73 (73.7 %)	Right	36 (49.3 %)
		Left	32 (43.9 %)
		Bilateral	5 (6.8 %)
	99 (100 %)	Do not describe laterality	29 (29.3 %)
	43 (43.4 %)	Multifocal	8 (18.5 %)
		Upper outer quadrant	22 (51.5 %)
		Lower outer quadrant	3 (6.8 %)
		Central	1 (2.3 %)
		Medial	9 (20.9 %)
Size of mass	35 (35.6 %)	Range 0.8–10 cm	
		Mean 3.82 cm	
		Median 3 cm	
	99 (100 %)	Do not described	64 (64.4 %)
Surgical management	99 (100 %)	Total patients who received surgery	65 (65.7 %)
	44 (44.4 %)	Mastectomy	8 (18.2 %)
		Partial Mastectomy/wide local excision	36 (81.8 %)
	21 (21.2 %)	Axillary Lymph Node Dissection	17(81 %)
		Sentinel Lymph Node Biopsy	4(19 %)
Medical management	38 (38.3 %)	Any adjuvant treatment	38 (38.3 %)
		Immunotherapy	15 (39.4 %)
		Cytotoxic	4 (10.5 %)
		Radiation	2(2 %)
		Not specified	21 (21.2 %)
Follow-up	21(21.2 %)	Range 1.5–70 months	
		Median 12 months	
		Mean 17.4 %	
Recurrence	7 (7.1 %)	Reported in only 7 patients (7.1 %)	
Survival	12 (12.1 %)	Mean 11.6 months	
		Median 11.5 months	
		Range 1–70 months	

metastatic breast carcinomas [43]. Thus, the use of a more specific marker, such as HMB-45 or Melan-A, may be more useful to confirm the diagnosis. These two markers are the most sensitive and specific markers for melanoma [41]. In one study of 67 primary melanomas, HMB-45 had a specificity of 100 % among malignant melanomas [42]. All but two of the cases described above were positive for another marker, with a 60 % rate of positive expression of HMB-45 and a 40 % rate for positive expression of Melan-A [41]. Five of the cases [6,17,21,29], presented amelanotic malignant melanoma, in which HMB-45 is debated to be less sensitive [41] Consequently, it is advised to test multiple melanocytic markers to achieve the correct diagnosis. In this case series, at least two thirds reported using IHC, with S-100 and HMB-45 being the most common positive stains confirming the diagnosis.

Nevertheless, ideally, a comprehensive IHC panel should be available to differentiate melanoma from other malignant tumors, such as carcinoma, including epithelial markers such as cytokeratins, EMA, with trichorhinophalangeal syndrome type 1 (TRPS1); and melanocytic markers such as the previously mentioned S100, and HMB-45, in addition to Melan A, vimentin, MART 1, SOX10 [36,44]. SOX10 is a nuclear transcription factor that is key in the differentiation of neural crest progenitor cells to melanocytes, and is currently considered a sensitive and specific marker for the diagnosis of malignant melanoma, while MART 1 regulates melanin synthesis [45]. Genetic mutations are also relevant, such as BRAF V600E, a intracellular kinase mutated in melanoma, which is key for targeted therapies.

It is challenging to differentiate melanoma from other malignant tumors in the breast. The fact that melanoma in breast tissue is a very rare clinical consideration and is often misdiagnosed as adenocarcinoma, pigmented epidermotropic breast carcinoma, or pigmented Paget disease, makes melanoma metastasis a diagnostic pitfall [30,46].Although clinical suspicion should arise when there is a previous history of melanoma, or rare clinical features are encountered, such as cutaneous compromised or contralateral axillary nodes without ipsilateral lymph node involvement [47], findings like nodular skin lesions, elevated lactate dehydrogenase levels, and normal Ca 15-3 levels [48]. Moreover, metastases to the breast are less fixed to breast tissue, more superficial, well circumscribed, round, and firm, without involvement of ducts, nipple retraction or discharge, and are usually solitary but may sometimes present diffuse involvement and rapid growth [9]. Moreover, imaging studies can show rounded or oval nodules with a well-defined posterior wall on ultrasound and well-defined nodular opacities without calcifications in mammography [23,49]. Although the final diagnosis is carried out by IHC and metastatic melanoma can mimic several cellular and architecture phenotypes, there are some histologic clues to indicate suspicion of melanoma; for example, the absence of an intraductal or lobular carcinoma component with the presence of lymphovascular invasion, melanin pigment within tumor cells, atypical epithelioid cells with prominent nucleoli, eccentric cytoplasm, or nuclear pseudoinclusions [38,44,50].

Multidisciplinary management of melanoma in breast tissue has demonstrated to be crucial due to the complexity of the pathological diagnosis, tumor biology, surgical treatment, oncogenic mutations, chromosomal aberrations, immune surveillance, neoadjuvant and adjuvant therapies, and targeted therapies, such as immunotherapy, to achieve better oncological and surgical outcomes with optimal quality of life [51,52]. When we reviewed surgical management after diagnosis, surgical interventions were offered in most cases (65 %) and were reported with multiple overlaps varying between ALND in the setting of mastectomies and breast-conserving surgery (PM/wide excision/segmental mastectomy). The most common procedure performed for loco-regional control of the tumor was PM along with axillary dissection of clinically positive nodes. Adjuvant therapy with heterogenous approaches was described in only 38 % of patients. Cases from last decade mentioned the most modern types of adjuvant immunotherapies. Neoadjuvant immunotherapy and checkpoint inhibitors were not mentioned, as their role in stage III and IV melanoma has only emerged in more recent years.

Survival and recurrence were difficult to quantify due to lack of reporting. The median survival of the 12 patients for whom this variable was reported was of close to one year from the time of breast tumor diagnosis. Two out of our 4 additional cases died within 2 and 6 months. Two patients are currently alive at 65 and 70 months of follow-up after surgical treatment of their breast tumors. Our patients present the longest survival reported; however, it is important to note that these are more recent patients who have had access to the newest first and second-line immunotherapies.

As the pathogenesis of MIBT is not well-established [6,18,53] and given that melanocytes do not reside in the breast parenchyma, the entity of MIBT relies on the following hypotheses One hypothesis postulates that neural crest cell precursors may have been carried into the glandular epithelium during the period of embryogenesis [54], or that it may be the result of a metaplastic transformation of a normal intramammary duct [55]. Others have hypothesized the presence of neoplastic genomic derepression describing the development of primary breast carcinoma with subsequent melanocytic differentiation [42]. The latest hypothesis describes a heterogeneous malignancy defined by the presence of carcinoma and melanoma within the same lesion [55]. Although the World Health Organization does not recognize this finding as a separate pathologic entity, five cases have been reported in the literature [56]. Nevertheless, this could represent the well-known and well-documented phenomenon of cancer-to-cancer metastases [57].

The argument against MIBT relies on the embryological development of the mammary glands and the well-known potential of malignant melanoma to metastasize to any organ in the body even decades after initial diagnosis. Therefore it is strongly believed that these melanotic tumors likely represent metastases rather than primary tumors [2]. This theory is supported by the findings of the present study, in which more than half of the patients were reported as having a previous cutaneous melanoma, with at least 40 % presenting positive axillary nodal and/or distant metastases in 30 %. This type of clinical history also supports the theory that these breast melanoma masses are the first site of recurrence by previously known or unknown melanomas. And even though metastatic disease to the breast by other tumors is extremely rare, ranging from 0.5 to 1.3 [58], cutaneous melanoma has previously been reported to be the most common origin of up to 30 % of metastatic tumors found in the breast [59].

Our series review supports the previous findings. However, melanoma can also recur after treatment, with thicker melanomas demonstrating recurrence rates of up to 58 %, and most likely involving lymph nodes [60]. Therefore, is well established that patients with a history of cutaneous melanoma who undergo surgical excision are also at risk of presenting regional or distant metastasis later in

life, sometimes even decades later [37]. In the institutional review of 27 patients with breast melanoma metastases by Ravdel et al. [15], all the patients had a history of malignant melanoma prior to the development of a mammary lesion, and in one case the breast mass was the first evidence of metastatic disease. Most of the patients presented with a palpable breast mass. In the Ravdel series, the median interval between the initial diagnoses and the finding of breast metastases was 52.5 months. In six of these patients, the disease presented from 10 to 18 years later. In our study, the median time from the presentation of the cutaneous melanoma to the presence of a breast mass was 65 months. Our case series presented the melanoma tumor from 2 to 12 years after initial diagnosis, being the first site of what was found to be a widely metastatic disease in lungs, liver, bones and with locoregional positive nodes in all 4 patients, in addition to in-transit metastasis in one of them.

In addition, the metastatic pathogenesis is supported by the presence of Intramammary lymph nodes completely replaced by tumor burden as in our cases. This confirms previous knowledge that in-transit intramammary lymph node metastases from melanoma can occur [6]. It is also well known that in approximately 5.6 % of patients with metastatic melanoma, the location of the primary tumor is unknown and in 65 % of these cases, the disease is limited to lymph nodes [61]. Lymph nodes can harbor aggregates of nevomelanocytes, including blue nevi (i.e., nodal blue nevus) [61]. These nevo-melanocytes are derived from the neural crest and are hypothesized to act as progenitors of melanoma [62]. In the first case, illustrated herein, the initial mammogram showed a stable, enlarged intramammary lymph node with no identifiable primary source. This explains the presentation of our first case. Two out of the 4 case reports, demonstrated the presence of in-transit intramammary nodal metastases in addition to positive axillary nodes.

In addition, cutaneous melanomas that have undergone complete regression, which is thought to occur as an immune response to melanoma [61], are usually not found but are associated with high rates of distant metastasis and early death [57,61]. All these findings emphasize the importance for clinicians to always examine patient history thoroughly and make an exhaustive clinical examination in search of primary melanoma in patients presenting intramammary melanotic or spindle cell masses.

Embryologically, melanotic lesions emerge in tissues that contain neural crest precursors such as the skin, mucosa, ears, leptomeningeal, and through the gastrointestinal tract [2]. The breast parenchyma lacks neural crest precursors [63]. The spread of metastasis may occur by direct lymphatic or vascular drainage. The rich blood supply and abundant glandular tissue of the breast may promote the transport of metastatic melanoma cells [9]. Moreover, estrogenic effects may contribute to the translocation of these metastatic cells into the breast parenchyma [64]. It has been postulated that the microenvironment of the breast and competency of the patient's immune system may confer a more aggressive presentation [65].

Therefore, based on all the above, we argue it is a misnomer to characterize these breast melanoma tumors as PMBP, and rather, they should be addressed as metastatic melanoma to the breast parenchyma. Pathology tests should be performed to identify the nodal capsule or in-transit component. It is important for these tumors to be reviewed in-depth by an experienced dermatopathologist. In our four additional cases, the true diagnosis was achieved by careful revaluation of the clinical history, imaging studies, and re-assessment of the pathological features, such as identification of the lymphatic cortex in the totally tumor-replaced intramammary node.

Management of breast melanoma without other sites of disease should be treated as stage III or IV disease based on appropriate staging. A thorough search for the primary lesion with a complete metastatic workup is always indicated, which should include brain MRI and whole-body PET or CT [8,61].

A multidisciplinary team approach must be considered and the surgical options for these patients need to be carefully planned and evaluated, as breast or axillary surgery may not necessarily eradicate the disease from a systemic standpoint, and the patient may be a candidate for neoadjuvant immunotherapy or included in clinical trials, prior to surgical resection, and tumors and axilla may even be down-staged.

Moreover, mastectomy has not shown to improve patient outcomes and therefore, it is not recommended as the surgical procedure of choice, although it may be necessary in cases in which the tumor burden does not allow breast-conserving surgery. The primary surgical treatment option should be complete surgical resection aimed at achieving negative margins. Management of regional nodes depends on the presence of clinical nodal involvement [8]. There is no role for sentinel lymph nodes in this scenario as the primary tumor does not originate in the breast but is rather another site of spread. Most reported cases show a high incidence of adjacent lymphadenopathy, supporting a more aggressive approach to axillary dissection for loco-regional control of the disease [66]. In this case series review, most patients presenting positive clinical nodal involvement underwent complete lymphadenectomy.

We recommend that clinically palpable lymph nodes be evaluated with ultrasound and those with radiographically suspicious morphological changes or positive on PET scan, should undergo ultrasound-guided core biopsy for tissue confirmation. Nodal basin management should include loco-regional control as per National Comprehensive Cancer Network guidelines [3]. In our case series, 60 % of patients in whom nodal status was reported did not have axillary lymph node metastases.

The current surgical recommendation for this pathology is wide local excision or PM of the primary site and sentinel lymph node biopsy without lymph node dissection [38]. Despite melanoma being considered as metastasis, when there is oligometastasis, following multidisciplinary consensus and adequate patient selection, patients undergoing metastasectomy have shown better long term survival rates, including longer disease-free survival, compared to those undergoing standard of care systemic therapies [67,68], while lymph node dissection has not demonstrated benefits in survival and is not recommended [69]. Prognosis should also be considered, identifying other markers, such as microsatellite, in-transit metastasis, other metastases, and BRAF mutational status.

Regarding radiotherapy, stereotactic radiosurgery has provided local disease control in pulmonary lesions and is considered an appropriate therapeutic option, which could be potentially extrapolated to breast metastasis [70]. Nowadays, the combination of several chemotherapy agents and biochemotherapy have shown higher toxicity rates without benefits in survival [71,72]. Neoadjuvant and/or adjuvant Immunotherapy is indicated in all patients with stage IIC, III, and IV metastatic melanomas [3]. These immunotherapies include ipilimumab, pembrolizumab, and nivolumab, which have been shown to prolong overall survival (OS) [73,74]. Anti-PD-1 monotherapy with nivolumab is recommended for advanced BRAF wild-type melanoma or combined with ipililumab

[73,75], an anti-CTLA4 agent. In addition, there is evidence showing pembrolizumab to have superior progression-free surgical (PFS) and overall survival (OS) compared to ipilimumab [74], and drugs such as atezolizumab have shown improved OS rates.

Molecular analyses are key for identifying oncogenic BRAFV600E, CKIT mutations in order to consider targeted therapies with the current developing BRAF, MEK inhibitor therapies [76], such as dabrafenib and trametinib against driver mutations in these patients [3]. These drugs have shown to improve PFS and OS [77,78] with tolerable toxicity profiles. All these therapies and studies are of potential interest for MIBT considered as a metastatic disease. Nonetheless, they should be considered with caution by a multidisciplinary tumor board to ensure the most adequate treatment and outcomes.

New emerging treatment modalities are under study and have shown promising outcomes in advanced and metastatic melanoma [68]. These include toll-like receptor therapies to promote intratumoral antigen cross-presentation that enhances antitumor response by adaptive immune cells [79], novel immune checkpoint inhibitors like the lymphocyte activation gene 3 [80], V domain immunoglobulin suppressor of T cell activation [81], T cell immunoglobulin and mucin domain 3 [82], cytokines such as IL-12 or IL-7, viral oncolytics [83], recombinant human granulocyte-macrophage colony-stimulating factor (GM CSF) [84], tyrosine kinase inhibitors [85], adoptive cellular therapy of tumor-infiltrating lymphocytes [86], engineered lymphocytes [87], antibody-dug conjugates [88], peptide vaccines [89], modification of microbiome [90], and antigen modulation like MAPK signaling pathways [91]. New ongoing clinical trials are performed around the world such as introduction of GM-CSF agents, biomarkers to indicate optimal timing to stop immunotherapies [92], cancer vaccines [93], high risk melanoma patients [94], between others.

The limitations of this review are inherent to the heterogeneity and retrospective nature of the data reported, as well the rarity of the cases. However, since this the largest review of the data currently available, we hope it encourages discussion among treating physicians, pathologists, and medical oncologists to provide multidisciplinary management for timely and appropriate treatment of patients and to challenge the concept of a primary breast source, as this implies important differences in patient management. A thorough dermatopathological analysis and pertinent IMC tests could help to obtain a more accurate diagnosis. Better understanding of genomic pathways and molecular markers is needed to further identify the true pathogenesis of this disease, and thereby help improve the diagnosis, treatment, and surveillance protocols and improve prognosis.

5. Conclusions

Melanoma of the breast parenchyma is rare. Although the true pathogenesis of these tumors remains to be elucidated, we believe the metastatic hypothesis is the most likely based on the embryological origin, the known metastatic phenotype, breast microenvironment, and clinical presentation. These tumors should be addressed as metastatic melanomas to the breast parenchyma. Staging, multidisciplinary management and thorough pathologic analyses are mandatory prior to surgical intervention. Treatment should include surgical excision of the tumor with negative margins and regional lymph node dissection of clinically positive nodes in the setting of neoadjuvant or adjuvant immunotherapy. Surgeons must be aware of this rare presentation, especially if the patient has a history of a previous cutaneous melanoma.

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Ethical statement

All study procedures received institutional ethical approval and informed consent was obtained as necessary.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Guarantor

All authors have reviewed and approved the final version of the manuscript. The corresponding author has complete access to all the data in the study and assumes complete responsibility for the integrity and accuracy of the data analysis. The lead author confirms that this manuscript provides an honest, accurate, and transparent account of the reported study, and that no crucial aspects of the study have been omitted.

CRediT authorship contribution statement

Alexis R. Narvaez-Rojas: Writing – review & editing, Supervision, Funding acquisition, Conceptualization. **Samantha Linhares:** Writing – original draft, Resources, Funding acquisition, Formal analysis, Conceptualization. **Shaina Sedighim:** Writing – original draft, Resources, Investigation, Formal analysis. **Kyle Daniel Klingbeil:** Visualization, Validation, Supervision, Resources, Project administration, Conceptualization. **Clara Milikowski:** Supervision, Resources, Project administration, Methodology. **George Elgart:** Validation, Supervision, Funding acquisition. **Natalia Jaimes:** Writing – original draft, Visualization, Validation, Resources, Methodology, Conceptualization. **Lynn Feun:** Writing – original draft, Validation, Supervision, Software, Methodology, Investigation,

Funding acquisition, Conceptualization. **Jose Lutzky:** Validation, Supervision, Software, Resources, Methodology, Formal analysis, Conceptualization. **Gabriel De la Cruz Ku:** Writing – review & editing, Writing – original draft, Visualization, Validation, Investigation, Formal analysis, Conceptualization. **Eli Avisar:** Validation, Methodology, Data curation, Conceptualization. **Mecker G. Möller:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Methodology, Investigation, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

[1] F. Bray, J. Ferlay, I. Soerjomataram, R.L. Siegel, L.A. Torre, A. Jemal, Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries, CA Cancer J Clin 68 (6) (2018) 394–424.
[2] W.E. Damsky, L.E. Rosenbaum, M. Bosenberg, Decoding melanoma metastasis, Cancers 3 (1) (2010) 126–163.
[3] National Comprehensive Cancer Network, Melanoma: cutaneous - NCCN guidelines. https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1492, 2023. (Accessed 21 April 2023).
[4] E. Maverakis, L. Cornelius, G. Bowen, T. Phan, F. Patel, S. Fitzmaurice, Y. He, B. Burrall, C. Duong, A. Kloxin, H. Sultani, R. Wilken, S. Martinez, F. Patel, Metastatic melanoma – a review of current and future treatment options, Acta Derm. Venereol. 95 (2014).
[5] J.B. Heistein, U. Acharya, S.K.R. Mukkamalla, Malignant melanoma, in: StatPearls [Internet], StatPearls Publishing, Treasure Island (FL), 2024 Jan [Updated 2023 May 22], https://www.ncbi.nlm.nih.gov/books/NBK470409/.
[6] M. Rassouli, I.A. Voutsadakis, Primary noncutaneous malignant melanoma of the breast, Breast J. 22 (6) (2016) 688–691.
[7] M.D. Howard, E. Wee, R. Wolfe, C.A. McLean, J.W. Kelly, Y. Pan, Anatomic location of primary melanoma: survival differences and sun exposure, J. Am. Acad. Dermatol. 81 (2) (2019) 500–509.
[8] M.M. Bernardo, M.J. Mascarenhas, D.P. Lopes, Primary malignant melanoma of the breast, Acta medica portuguesa 2 (1) (1980) 39–43.
[9] B. Vergier, M. Trojani, I. de Mascarel, J.M. Coindre, A. Le Treut, Metastases to the breast: differential diagnosis from primary breast carcinoma, J. Surg. Oncol. 48 (2) (1991) 112–116.
[10] J. Cangiarella, W.F. Symmans, J.M. Cohen, A. Goldenberg, R.L. Shapiro, J. Waisman, Malignant melanoma metastatic to the breast: a report of seven cases diagnosed by fine-needle aspiration cytology, Cancer 84 (3) (1998) 160–162.
[11] G. Kobayashi, C. Cobb, A case of amelanotic spindle-cell melanoma presenting as metastases to breast and axillary lymph node: diagnosis by FNA cytology, Diagn. Cytopathol. 22 (4) (2000) 246–249.
[12] T. Kim, M. Chae, H. Kim, S.Y. Kim, M. Baek, M. Lee, C. Kim, E. Kim, M. Lee, M. Cho, O. Song, A case of malignant melanoma presenting as a breast mass, Journal of Korean Breast Cancer Society 6 (2003) 35.
[13] E. Mayayo Artal, V. Gómez-Aracil, R. Mayayo Alvira, J. Azua-Romeo, A. Arraiza, Spindle cell malignant melanoma metastatic to the breast from a pigmented lesion on the back. A case report, Acta Cytol. 48 (3) (2004) 387–390.
[14] A. Loffeld, J.R. Marsden, Management of melanoma metastasis to the breast: case series and review of the literature, Br. J. Dermatol. 152 (6) (2005) 1206–1210.
[15] L. Ravdel, W.A. Robinson, K. Lewis, R. Gonzalez, Metastatic melanoma in the breast: a report of 27 cases, J. Surg. Oncol. 94 (2) (2006) 101–104.
[16] A. Vaughan, J.R. Dietz, J.F. Moley, M.K. Debenedetti, R.L. Aft, W.E. Gillanders, T.J. Eberlein, J. Ritter, J.A. Margenthaler, Metastatic disease to the breast: the Washington University experience, World J. Surg. Oncol. 5 (2007) 74.
[17] S. Roy, K. Dhingra, S. Mandal, N. Khurana, Unusual presentation of metastatic amelanotic melanoma of unknown primary origin as a solitary breast lump, Melanoma Res. 18 (6) (2008) 447–450.
[18] M. Uludag, B. Citgez, O. Ozkaya, D. Sakiz, In-transit metastasis of the breast region from malignant melanoma of the trunk, BMJ Case Rep. 2009 (2009).
[19] A. Al Samaraee, H. Khout, T. Barakat, T. Fasih, Breast metastasis from a melanoma, Ochsner J. 12 (2) (2012) 149–151.
[20] C.E. Bacchi, S.C. Wludarski, A.B. Ambaye, J. Lamovec, T. Salviato, G. Falconieri, Metastatic melanoma presenting as an isolated breast tumor: a study of 20 cases with emphasis on several primary mimickers, Archives of pathology & laboratory medicine 137 (1) (2013) 41–49.
[21] A. Biswas, S. Goyal, A. Jain, V. Suri, S. Mathur, P.K. Julka, G.K. Rath, Primary amelanotic melanoma of the breast: combating a rare cancer, Breast cancer (Tokyo, Japan) 21 (2) (2014) 236–240.
[22] Y. He, J. Mou, D. Luo, B. Gao, Y. Wen, Primary malignant melanoma of the breast: a case report and review of the literature, Oncol. Lett. 8 (1) (2014) 238–240.
[23] M. Moschetta, M. Telegrafo, N.M. Lucarelli, G. Martino, L. Rella, A.A. Stabile Ianora, G. Angelelli, Metastatic breast disease from cutaneous malignant melanoma, International journal of surgery case reports 5 (1) (2014) 34–36.
[24] J.A. Vasudevan, T. Somanathan, A. Mathews, J. Kattoor, Malignant melanoma of breast: a unique case with diagnostic dilemmas, Indian J. Pathol. Microbiol. 57 (2) (2014) 287–289.
[25] S. Srikanth, G. Anandam, Malignant melanoma of male breast with nodal metastasis, Medical Journal of Dr, D.Y. Patil University 7 (2) (2014).
[26] D. Drueppel, B. Schultheis, W. Solass, H. Ergonenc, C.B. Tempfer, Primary malignant melanoma of the breast: case report and review of the literature, Anticancer research 35 (3) (2015) 1709–1713.
[27] Z. El-Tani, C. Duc, T. Gluecker, O. Cottier, Intramammary metastatic melanoma of unknown primary origin in a 58-year old patient: a case report, J. Med. Case Rep. 10 (1) (2016) 363.
[28] L. Feng, D.J. Qi, Q.F. Zhang, Anorectal melanoma metastatic to the breast: a case report and review of the literature, OncoTargets Ther. 9 (2016) 4969–4974.
[29] P. Sathiah, D. Gochhait, S. Adithan, S. Umamahesweran, P. Dehuri, Amelanotic signet ring cell melanoma presenting as breast lump- A diagnostic conundrum, J. Clin. Diagn. Res. : J. Clin. Diagn. Res. 11 (8) (2017) Ed08–ed10.
[30] J. Koh, J. Lee, S.Y. Jung, H.S. Kang, T. Yun, Y. Kwon, Primary malignant melanoma of the breast: a report of two cases, Journal of pathology and translational medicine 53 (2) (2019) 119–124.
[31] A. Mastoraki, A. Gkiala, G. Theodoroleas, E. Mouchtouri, A. Strimpakos, D. Papagiannopoulou, D. Schizas, Metastatic malignant melanoma of the breast: report of a case and review of the literature 64 (2) (2022) 354–358.
[32] E. Snashall, T. Kiernan, A. Harper-Machin, R. Taghizadeh, Primary melanoma of the breast parenchyma: an oncoplastic approach, Plastic and reconstructive surgery. Global open 8 (12) (2020) e3276.
[33] T. Do, R. Epistola, D.T. Hua, M.M. Taylor, R. Venegas, Diagnostic delays in metastatic amelanotic melanoma presenting as breast pain, The American journal of case reports 21 (2020) e921360.

[34] S. Sharma, D.S. Long, S. Sharma, Metastatic melanoma presenting as a breast mass - role of radiologist as a clinician, Radiology case reports 15 (10) (2020) 2031–2035.
[35] R.M. Harsten, R. Fisher, N. Al-Sanjari, P. Idaewor, A. Saad Abdalla Al-Zawi, Metastatic malignant melanoma with occult primary presenting as breast mass: a case report and literature review, Cureus 13 (6) (2021) e15886.
[36] D. Ai, J. Yao, F. Yang, TRPS1: a highly sensitive and specific marker for breast carcinoma, especially for triple-negative, breast cancer 34 (4) (2021) 710–719.
[37] H. Yen, B. Florentine, L.K. Kelly, X. Bu, J. Crawford, S.E. Martin, Fine-needle aspiration of a metaplastic breast carcinoma with extensive melanocytic differentiation: a case report, Diagn. Cytopathol. 23 (1) (2000) 46–50.
[38] S. Kurul, F. Taş, N. Büyükbabani, A. Mudun, C. Baykal, H. Camlica, Different manifestations of malignant melanoma in the breast: a report of 12 cases and a review of the literature, Jpn. J. Clin. Oncol. 35 (4) (2005) 202–206.
[39] C.C. McLaughlin, X.C. Wu, A. Jemal, H.J. Martin, L.M. Roche, V.W. Chen, Incidence of noncutaneous melanomas in the U.S, Cancer 103 (5) (2005) 1000–1007.
[40] K. Blessing, D.S. Sanders, J.J. Grant, Comparison of immunohistochemical staining of the novel antibody melan-A with S100 protein and HMB-45 in malignant melanoma and melanoma variants, Histopathology 32 (2) (1998) 139–146.
[41] S.J. Ohsie, G.P. Sarantopoulos, A.J. Cochran, S.W. Binder, Immunohistochemical characteristics of melanoma, J. Cutan. Pathol. 35 (5) (2008) 433–444.
[42] INVALID CITATION !!!).
[43] S. Dwarakanath, A.K. Lee, R.A. Delellis, M.L. Silverman, L. Frasca, H.J. Wolfe, S-100 protein positivity in breast carcinomas: a potential pitfall in diagnostic immunohistochemistry, Hum. Pathol. 18 (11) (1987) 1144–1148.
[44] M.A. John, N. Pourfarrokh, J.R. Asirvatham, Melanoma in the breast: a diagnostic challenge, Yale J. Biol. Med. 96 (4) (2023) 475–479.
[45] M.S. Hsieh, Y.H. Lee, Y.L. Chang, SOX10-positive salivary gland tumors: a growing list, including mammary analogue secretory carcinoma of the salivary gland, sialoblastoma, low-grade salivary duct carcinoma, basal cell adenoma/adenocarcinoma, and a subgroup of mucoepidermoid carcinoma, Hum. Pathol. 56 (2016) 134–142.
[46] I. Rolim, M. Rafael, A. Robson, J. Costa Rosa, Pigmented epidermotropic breast carcinoma: a diagnostic pitfall mimicking melanoma A case report and literature review, Int. J. Surg. Pathol. 32 (2) (2024) 386–393.
[47] S.K. Lee, W.W. Kim, S.H. Kim, S.M. Hur, S. Kim, J.H. Choi, E.Y. Cho, S.Y. Han, B.K. Hahn, J.H. Choe, J.H. Kim, J.S. Kim, J.E. Lee, S.J. Nam, J.H. Yang, Characteristics of metastasis in the breast from extramammary malignancies, J. Surg. Oncol. 101 (2) (2010) 137–140.
[48] G. Bahat, Y. Colak, B. Saka, M.A. Karan, N. Buyukbabani, Melanoma metastasis to the breast: a diagnostic pitfall, Cancer Detect. Prev. 32 (5–6) (2009) 458–461.
[49] J. Majeski, Bilateral breast masses as initial presentation of widely metastatic melanoma, J. Surg. Oncol. 72 (3) (1999) 175–177.
[50] P. Das, N. Kumar, A. Ahuja, A. Jain, R. Ray, C. Sarkar, S.D. Gupta, Primary malignant melanoma at unusual sites: an institutional experience with review of literature, Melanoma Res. 20 (3) (2010) 233–239.
[51] M.A. McKean, R.N. Amaria, Multidisciplinary treatment strategies in high-risk resectable melanoma: role of adjuvant and neoadjuvant therapy, Cancer Treat Rev. 70 (2018) 144–153.
[52] A. Fortuna, T. Amaral, Multidisciplinary approach and treatment of acral and mucosal melanoma, Front. Oncol. 14 (2024) 1340408.
[53] S.E. Stephenson Jr., B.F. Byrd Jr., Malignant melanoma of the breast, Am. J. Surg. 97 (2) (1959) 232–235.
[54] L.H. Maguire, A.R. Thomas, A.M. Goldstein, Tumors of the neural crest: common themes in development and cancer, Dev. Dynam. : an official publication of the American Association of Anatomists 244 (3) (2015) 311–322.
[55] A. Bendic, M. Bozic, M.G. Durdov, Metaplastic breast carcinoma with melanocytic differentiation, Pathol. Int. 59 (9) (2009) 676–680.
[56] P.B. Chapman, A. Hauschild, C. Robert, J.B. Haanen, P. Ascierto, J. Larkin, R. Dummer, C. Garbe, A. Testori, M. Maio, D. Hogg, P. Lorigan, C. Lebbe, T. Jouary, D. Schadendorf, A. Ribas, S.J. O'Day, J.A. Sosman, J.M. Kirkwood, A.M. Eggermont, B. Dreno, K. Nolop, J. Li, B. Nelson, J. Hou, R.J. Lee, K.T. Flaherty, G. A. McArthur, Improved survival with vemurafenib in melanoma with BRAF V600E mutation, N. Engl. J. Med. 364 (26) (2011) 2507–2516.
[57] M.G. Möller, T. Gribbin, S. Ebrom, G. Padula, T.L. Fitzgerald, Breast cancer metastatic to renal cell carcinoma, Surgery 139 (4) (2006) 577–579.
[58] S.H. Mun, E.Y. Ko, B.K. Han, J.H. Shin, S.J. Kim, E.Y. Cho, Breast metastases from extramammary malignancies: typical and atypical ultrasound features, Korean J. Radiol. 15 (1) (2014) 20–28.
[59] A. Koch, A. Richter-Marot, M.P. Wissler, A. Baratte, C. Mathelin, [Mammary metastasis of extramammary cancers: current knowledge and diagnostic difficulties], Gynecol. Obstet. Fertil. 41 (11) (2013) 653–659.
[60] A. Alzaraa, N. Sharma, Primary cutaneous melanoma of the breast: a case report, Cases journal 1 (2008) 212.
[61] A.E. Giuliano, A.J. Cochran, D.L. Morton, Melanoma from unknown primary site and amelanotic melanoma, Semin. Oncol. 9 (4) (1982) 442–447.
[62] B.V. Shenoy, L. Fort 3rd, S.P. Benjamin, Malignant melanoma primary in lymph node. The case of the missing link, Am. J. Surg. Pathol. 11 (2) (1987) 140–146.
[63] A. Javed, A. Lteif, Development of the human breast, Semin. Plast. Surg. 27 (1) (2013) 5–12.
[64] F. Bassi, G. Gatti, E. Mauri, B. Ballardini, T. De Pas, A. Luini, Breast metastases from cutaneous malignant melanoma, Breast 13 (6) (2004) 533–535.
[65] L.E.L. Terceiro, C.A. Edechi, N.M. Ikeogu, B.E. Nickel, S. Hombach-Klonisch, T. Sharif, E. Leygue, The breast tumor microenvironment: a key player in metastatic spread 13 (19) (2021).
[66] A. Asaad, A.S. Abdalla, P. Idaewor, B. Jayasooryia, V. Yates, S. Eldruki, J. English, Breast metastasis as a presentation of malignant melanoma, Chirurgia 113 (5) (2018) 712–718.
[67] A.C. Gamboa, M. Lowe, M.L. Yushak, K.A. Delman, Surgical considerations and systemic therapy of melanoma, Surg. Clin. 100 (1) (2020) 141–159.
[68] B. Switzer, I. Puzanov, Managing metastatic melanoma in 2022: a clinical review 18 (5) (2022) 335–351.
[69] M. Sladden, S. Zagarella, C. Popescu, M. Bigby, No survival benefit for patients with melanoma undergoing sentinel lymph node biopsy: critical appraisal of the Multicenter Selective Lymphadenectomy Trial-I final report, Br. J. Dermatol. 172 (3) (2015) 566–571.
[70] D.A. Palma, R. Olson, S. Harrow, S. Gaede, A.V. Louie, C. Haasbeek, L. Mulroy, M. Lock, G.B. Rodrigues, B.P. Yaremko, D. Schellenberg, B. Ahmad, S. Senthi, A. Swaminath, N. Kopek, M. Liu, K. Moore, S. Currie, R. Schlijper, G.S. Bauman, J. Laba, X.M. Qu, A. Warner, S. Senan, Stereotactic ablative radiotherapy for the comprehensive treatment of oligometastatic cancers: long-term results of the SABR-COMET phase II randomized trial, J. Clin. Oncol. : official journal of the American Society of Clinical Oncology 38 (25) (2020) 2830–2838.
[71] P.B. Chapman, L.H. Einhorn, M.L. Meyers, S. Saxman, A.N. Destro, K.S. Panageas, C.B. Begg, S.S. Agarwala, L.M. Schuchter, M.S. Ernstoff, A.N. Houghton, J. M. Kirkwood, Phase III multicenter randomized trial of the dartmouth regimen versus dacarbazine in patients with metastatic melanoma, J. Clin. Oncol. 17 (9) (1999), 2745-2745.
[72] N.J. Ives, R.L. Stowe, P. Lorigan, K. Wheatley, Chemotherapy compared with biochemotherapy for the treatment of metastatic melanoma: a meta-analysis of 18 trials involving 2,621 patients, J. Clin. Oncol. : official journal of the American Society of Clinical Oncology 25 (34) (2007) 5426–5434.
[73] J. Larkin, V. Chiarion-Sileni, R. Gonzalez, J.-J. Grob, P. Rutkowski, D. Lao Christopher, C.L. Cowey, D. Schadendorf, J. Wagstaff, R. Dummer, F. Ferrucci Pier, M. Smylie, D. Hogg, A. Hill, I. Márquez-Rodas, J. Haanen, M. Guidoboni, M. Maio, P. Schöffski, S. Carlino Matteo, C. Lebbé, G. McArthur, A. Ascierto Paolo, A. Daniels Gregory, V. Long Georgina, L. Bastholt, I. Rizzo Jasmine, A. Balogh, A. Moshyk, F.S. Hodi, D. Wolchok Jedd, Five-year survival with combined nivolumab and ipilimumab in advanced melanoma, N. Engl. J. Med. 381 (16) (2019) 1535–1546.
[74] C. Robert, A. Ribas, J. Schachter, A. Arance, J.J. Grob, L. Mortier, A. Daud, M.S. Carlino, C.M. McNeil, M. Lotem, J.M.G. Larkin, P. Lorigan, B. Neyns, C.U. Blank, T.M. Petrella, O. Hamid, S.C. Su, C. Krepler, N. Ibrahim, G.V. Long, Pembrolizumab versus ipilimumab in advanced melanoma (KEYNOTE-006): post-hoc 5-year results from an open-label, multicentre, randomised, controlled, phase 3 study, Lancet Oncol. 20 (9) (2019) 1239–1251.
[75] F.S. Hodi, S.J. O'Day, D.F. McDermott, R.W. Weber, J.A. Sosman, J.B. Haanen, R. Gonzalez, C. Robert, D. Schadendorf, J.C. Hassel, W. Akerley, A.J. van den Eertwegh, J. Lutzky, P. Lorigan, J.M. Vaubel, G.P. Linette, D. Hogg, C.H. Ottensmeier, C. Lebbé, C. Peschel, I. Quirt, J.I. Clark, J.D. Wolchok, J.S. Weber, J. Tian, M.J. Yellin, G.M. Nichol, A. Hoos, W.J. Urba, Improved survival with ipilimumab in patients with metastatic melanoma, N. Engl. J. Med. 363 (8) (2010) 711–723.
[76] G.V. Long, C. Lebbe, V. Atkinson, M. Mandalà, P.D. Nathan, A.N.A.M. Arance Fernandez, E. Richtig, N. Yamazaki, C. Robert, D. Schadendorf, H.A.-H. Tawbi, P. A. Ascierto, A. Ribas, K. Flaherty, D.-Y. Lee, A. Masood, E. Gasal, R. Dummer, The anti–PD-1 antibody spartalizumab (S) in combination with dabrafenib (D) and

trametinib (T) in previously untreated patients (pts) with advanced BRAF V600–mutant melanoma: updated efficacy and safety from parts 1 and 2 of COMBI-i, J. Clin. Oncol. 37 (15_suppl) (2019), 9531-9531.
[77] G.V. Long, A. Hauschild, M. Santinami, V. Atkinson, M. Mandalà, V. Chiarion-Sileni, J. Larkin, M. Nyakas, C. Dutriaux, A. Haydon, C. Robert, L. Mortier, J. Schachter, D. Schadendorf, T. Lesimple, R. Plummer, R. Ji, P. Zhang, B. Mookerjee, J. Legos, R. Kefford, R. Dummer, J.M. Kirkwood, Adjuvant dabrafenib plus trametinib in stage III BRAF-mutated melanoma, N. Engl. J. Med. 377 (19) (2017) 1813–1823.
[78] P.A. Ascierto, G.V. Long, C. Robert, B. Brady, C. Dutriaux, A.M. Di Giacomo, L. Mortier, J.C. Hassel, P. Rutkowski, C. McNeil, E. Kalinka-Warzocha, K.J. Savage, M.M. Hernberg, C. Lebbé, J. Charles, C. Mihalcioiu, V. Chiarion-Sileni, C. Mauch, F. Cognetti, L. Ny, A. Arance, I.M. Svane, D. Schadendorf, H. Gogas, A. Saci, J. Jiang, J. Rizzo, V. Atkinson, Survival outcomes in patients with previously untreated BRAF wild-type advanced melanoma treated with nivolumab therapy: three-year follow-up of a randomized phase 3 trial, JAMA Oncol. 5 (2) (2019) 187–194.
[79] K. Kapp, B. Volz, D. Oswald, B. Wittig, M. Baumann, M. Schmidt, Beneficial modulation of the tumor microenvironment and generation of anti-tumor responses by TLR9 agonist lefitolimod alone and in combination with checkpoint inhibitors, OncoImmunology 8 (12) (2019) e1659096.
[80] H.A. Tawbi, D. Schadendorf, Relatlimab and nivolumab versus nivolumab in untreated advanced melanoma 386 (1) (2022) 24–34.
[81] J. Choi, Y. Kim, K. Yun, C.H. Won, m.w. Lee, J. Choi, S. Chang, W. Lee, The prognostic significance of VISTA and CD33-positive myeloid cells in cutaneous melanoma and their relationship with PD-1 expression, Sci. Rep. 10 (2020).
[82] N. Acharya, C. Sabatos-Peyton, A.C. Anderson, Tim-3 finds its place in the cancer immunotherapy landscape 8 (1) (2020).
[83] F.F. Gellrich, M. Schmitz, S. Beissert, F. Meier, Anti-PD-1 and novel combinations in the treatment of melanoma-an update, J. Clin. Med. 9 (1) (2020).
[84] S.S. Ring, J. Cupovic, L. Onder, M. Lütge, Viral vector-mediated reprogramming of the fibroblastic tumor stroma sustains curative melanoma treatment 12 (1) (2021) 4734.
[85] S. Jung, E. Armstrong, A. Wei, F. Ye, A. Lee, M. Carlino, R. Sullivan, R. Carvajal, A. Shoushtari, D. Johnson, Clinical and genomic correlates of imatinib response in melanomas with KIT alterations, British journal of cancer 127 (2022).
[86] A. Villani, M. Scalvenzi, G. Fabbrocini, J. Ocampo-Candiani, S.S. Ocampo-Garza, Looking into a better future: novel therapies for metastatic melanoma, Dermatology and therapy 11 (3) (2021) 751–767.
[87] A.D. Waldman, J.M. Fritz, M.J. Lenardo, A guide to cancer immunotherapy: from T cell basic science to clinical practice 20 (11) (2020) 651–668.
[88] Y. Tanaka, T. Ito, Human epidermal growth factor receptor 3 serves as a novel therapeutic target for acral melanoma 9 (1) (2023) 54.
[89] J.W. Kjeldsen, C.L. Lorentzen, E. Martinenaite, E. Ellebaek, A phase 1/2 trial of an immune-modulatory vaccine against Ido/PD-L1 in combination with nivolumab in metastatic melanoma 27 (12) (2021) 2212–2223.
[90] X. Li, S. Zhang, G. Guo, J. Han, J. Yu, Gut microbiome in modulating immune checkpoint inhibitors, EBioMedicine 82 (2022).
[91] M. Khaliq, M. Manikkam, E.D. Martinez, Epigenetic modulation reveals differentiation state specificity of oncogene addiction 12 (1) (2021) 1536.
[92] National Cancer Institute. Using Biomarkers to Help Guide Safe Immunotherapy Discontinuation in Patients with Unresectable Stage IIIB-IV Melanoma, The PET-Stop Trial. NCI-Supported Clinical Trials. Available in: https://www.cancer.gov/research/participate/clinical-trials-search/v?id=NCI-2020-04463&r=1.
[93] National Cancer Institute. An Efficacy Study of Adjuvant Treatment With the Personalized Cancer Vaccine mRNA-4157 and Pembrolizumab in Participants With High-Risk Melanoma (KEYNOTE-942). NCI-Supported Clinical Trials. Available in: https://www.cancer.gov/research/participate/clinical-trials-search/v?id=NCI-2019-04957&r=1.
[94] National Cancer Institute. A Study of Adjuvant Pembrolizumab/Vibostolimab (MK-7684A) Versus Pembrolizumab for Resected High-Risk Melanoma in Participants With High-Risk Stage II-IV Melanoma (MK-7684A-010/KEYVIBE-010). NCI-Supported Clinical Trials. Available in: https://www.cancer.gov/research/participate/clinical-trials-search/v?id=NCI-2023-02088&r=1.