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Unusual metastases of breast cancer: a single-center retrospective study

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ABSTRACT

Objectives: While clinical and radiological awareness of the usual, frequent metastatic sites of breast cancer is high, unexpected 'atypical' localisations may be more easily overlooked in the cancer management process. The aim of this article is to contribute to this awareness in order to facilitate and improve the diagnosis and follow-up of breast cancer.

Methods: In this study, we retrospectively evaluated breast cancer patients who were diagnosed and followed up between 2017 and 2022 in our hospital, which is an important oncology center.

Results: Of the 852 patients included in this study, 79 had an unusual metastasis localization. The most common unusual metastasis sites were mediastinal lymph nodes and brain. These sites were followed by atypical bone involvement, mesenteric lymph nodes, cervical lymph nodes, hilar lymph nodes and surrenal metastases. The most rare metastases were more common in the uterus and ovary, followed by pancreas, parotid gland, spleen, colon, pericardium-atrium, orbital soft tissues and lacrimal gland. The unusual site of metastasis was mediastinal lymph nodes in 17.7% (n = 14), brain in 17.7% (n = 14), atypical bone sites in 12.6% (n = 10), mesenteric lymph nodes in 11.3% (n = 9), cervical lymph nodes in 11.3% (n = 9), hilar lymph nodes in 5% (n = 4) and surrenal in 6.3% (n = 5).

Conclusions: Sharing knowledge and experience about unusual metastases of breast cancer will contribute to the diagnosis and treatment of metastatic diseases by increasing the awareness of this issue. For this, multicentre studies should be conducted to combine these experiences.

Keywords: Breast cancer, unusual metastases, rare metastases, atypical metastases

Breast cancer is a very common malignant tumour and metastatic disease is still the leading cause of death in breast cancer patients. Today, the rate of metastasis is increasing even in regions known to be rare. This is due to more effective treatments that prolong the overall life expectancy of breast cancer patients and the progress made in early diagnosis thanks to the development of new imaging techniques [1]. However, since it is still possible to encounter metastatic disease in breast cancer patients even after many years, the evaluation of each symptom reported by a breast cancer patient can lead us to a conclusion that may affect survival by detecting a metatastic focus early. Therefore, knowing even the rare metastatic

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sites of breast cancer will help clinically correct interpretation of new symptoms and selection of correct diagnostic techniques in patients followed up for breast cancer [2]. The aim of this article is to increase the awareness of every physician in the chain of physicians involved in the diagnosis and follow-up of breast cancer patients about the presence of unusual metastases by sharing our own experience of unusual metastases in breast cancer patients in our center.

METHODS

In this study, we retrospectively evaluated breast cancer patients who were diagnosed and followed up between 2017 and 2022 in our hospital, which is an important oncology center. Among these patients, we included 852 patients for whom we could obtain complete patient information from hospital notes and access to radiological computed tomography (CT) and magnetic resonance imaging (MRI) images from the hospital radiology archive system (PACS), and excluded other patients with missing patient information or imaging findings. Of the 852 patients included in the study, 12 were missing imaging findings, and 10 were missing information on one or more receptor subtypes.

Statistical Analysis

Analyses were performed using SPSS Version 23.0 (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY). A two-tailed Kolmogorov-Smirnov test was applied to examine for whether the continuous quantitative variables follow a Gaussian distribution. Characteristics of patients, as n (percent) or median (minimum-maximum) for categorical and continuous variables, respectively, and were compared among treatment groups using chi-square or Mann-Whitney tests, as appropriate. A p value was set at < 0.05 for statistical significance.

RESULTS

Of the 852 patients included in this study, 79 had an unusual metastasis localisation. The unusual site of metastasis was mediastinal lymph nodes in 17.7% (n = 14), brain in 17.7% (n = 14), atypical bone sites in 12.6% (n = 10), mesenteric lymph nodes in 11.3% (n = 9), cervical lymph nodes in 11.3% (n = 9), hilar lymph nodes in 5% (n = 4) and surrenal in 6.3% (n = 5). In our retrospective analysis, some of the unusual metastasis sites included in our cohort; parathyroid involvement, orbital involvement, mandibular involvement, metastasis to the surrenal gland, pancreas, and ovaries are shown in Fig. 1.

The remaining 28.7% of the unusual metastases were rarer metastases and were as follows; two patients had uterus and ovary involvement, two patients had only ovarian metastatic mass, two patients had spleen metastasis, one patient had pancreas metastasis, one patient had pericardium and atrium metastasis, one patient had parotid metastasis, one patient had orbit metastasis and one patient had colon and endobronchial involvement. When we made a comparison between breast cancer groups with and without unusual metastasis in terms of age and tumour stage, 8.3% (16 patients) in Grade I and 10.3% (68 patients) in Grade II-III had unusual metastasis and there was no statistically significant difference between these two groups (Table 1).

We also divided the patients into two groups as invasive ductal carcinoma and lobular carcinoma, which are the two main histopathological subtypes, and examined the relationship between these two groups and the presence of unusual metastasis. There were 71 (10.1%) unusual metastases in the invasive ductal carcinoma group and 6 (9.8%) unusual metastases in the invasive lobular carcinoma group. Since the number of cases in some of the foci with unusual metastases was very small (in some localisations there was only one patient), we could not look at the relationship between histopathological subtypes and unusual metastases in each localisation and histopathological subtype. We further divided the patients into four receptor subgroups; group 1: Estrogen receptor (ER) and/or progesteron receptor (PR) (+), human epidermal growth factor receptor 2 (CERB) (-); group 2: ER and/or PR (+), CERB (+); group 3: ER (-), PR (-), CERB (-) and group 4: ER (-), PR (-), CERB (+). There were 42 (9.3%) patients in ER and/or PR (+), CERB (-), 30 (12.1%) patients in ER and/or PR (+), CERB (+), 11 (12.8%) patients in ER (-), PR (-), CERB (-) and 1 (15%) patient in ER (-), PR (-), CERB (+) (Table 2).

There was a statistically significant difference in

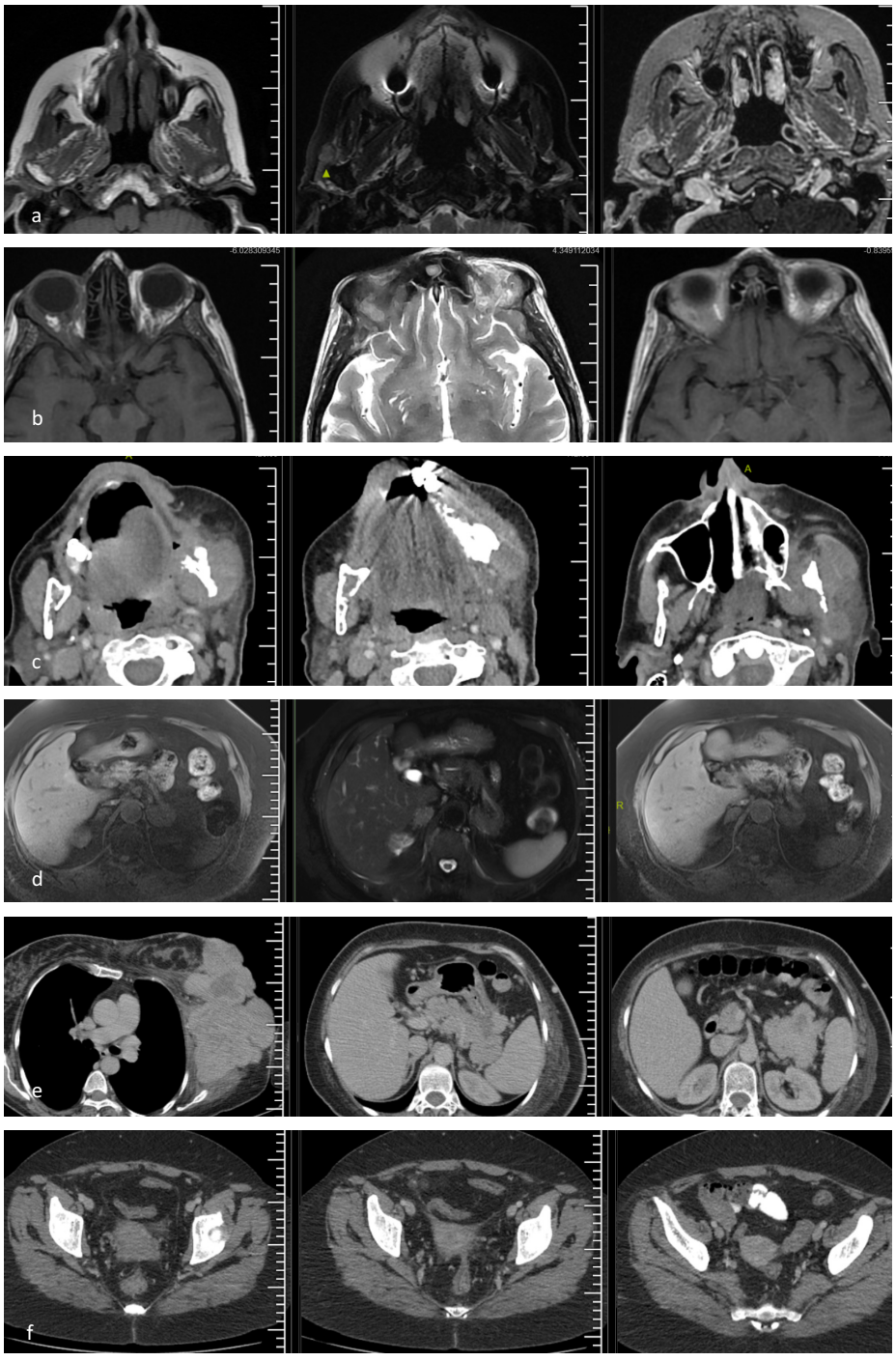

Fig. 1. (a) Anterior part of the superficial lobe of the right parotid gland showing hypointense signal on T1-weighted sequences and isointense signal with the parotid gland on T2-weighted sequences, showing peripheral weighted contrast enhancement after IVKM, nodular lesion, (b) A metastatic focus with isointense on T1-weighted sequences and increased intensity on T2-weighted sequences, with mild oedematous sinya extraconal distance and lacrimal gland and upper eyelid level on STIR sequence, extending from the right orbital apex laterally to the retrobulbar area, (c) Left mandibular corpus containing an expansile sclerotic component extending towards the mandibular angulus and causing fractures at the level of the mandibular angulus condyle in places, also metastatic focus with a soft tissue component with a thickness of approximately 10 mm extending into the masseter muscle, (d) Hyperintense in T2A series and hypointense in T1A series in the localisation of the right surrenal lobe body and left surrenal gland body, metastatic lesions with contrast enhancement in early phases, contrast release in late phases and diffusion restriction after IVKM in dynamic series, (e) Metastatic lesion with cystic-necrotic areas approximately 36×24 mm in the tail of the pancreas with unclear borders and (f) Both ovaries contain heteogenous hypodense masses with increased size.

Table 1. Distribution of unusual metastasis sites of the participants

Metastasis sites (n = 79)	n	%
Mediastinal lymph nodes	14	17.7
Brain	14	17.7
Atypical bone metastasis	10	12.6
Mesenteric lymph nodes	9	11.3
Cervical lymph nodes	9	11.3
Hilar lymph nodes	4	5.0
Surrenal	5	6.3
Others	12	28.7

terms of age between the patient groups with and without unusual metastasis (p = 0.005). In addition, there was a statistically significant correlation between metastasis groups and receptor groups (p = 0.023), while there was no significant correlation with tumor types (p = 1.000) (see Table 2).

DISCUSSION

Today, breast cancer still occupies an important place in the cancer agenda of the scientific world as a disease that is the main cause of cancer deaths in women, maintains its top position in cancer statistics with more than one million new diagnoses per year and increases cancer treatment costs. As in all cancer types, the presence of metastasis in breast cancer, its onset and course of development cannot be predicted and its determinant effect on the patient's clinic increases exponentially, the presence of metastasis remains the main challenge to be overcome in the war against breast cancer [3].

Like all other malignancies, the evolution of tumour metastasis in breast cancer is still controversial. Starting with Paget's "seed and soil" hypothesis, numerous studies have confirmed his findings and integrated the idea of a multi-stage process in which tumour cells, like a seed, are nourished and grow when they meet a fertile soil, in which both the tumour cell and the host are active. Findings that translate Paget's theory into clinical practice show that breast cancer preferentially spreads to some organs at a much higher rate, while it is less common to encounter breast cancer metastasis in some remote areas. In this study, we focussed mainly on anatomical regions where few metastasis rates have been reported in the literature [1].

According to many studies, distant metastases of

Table 2. Distribution of demographic and clinical findings according to unusual metastasis development

Variables	Unusual metastasis		
	Yes (n = 79)	No (n = 773)	*p* value
Age (years)	50 (25-85)	53 (22-88)	**0.005**
Tumor grade, n (%)			0.820
Grade I	17 (21.5)	175 (22.6)	
Grade II-III	62 (78.5)	598 (77.4)	
Receptor group, n (%)			**0.023**
ER and/or PR (+), CERB (-)	30 (38.0)	424 (54.9)	
ER and/or PR (+), CERB (+)	33 (41.8)	212 (27.4)	
ER (-), PR (-), CERB (-)	8 (10.1)	78 (10.1)	
ER (-), PR (-), CERB (+)	8 (10.1)	59 (7.6)	
Tumor type, n (%)			1.000
Invasive ductal	67 (91.8)	633 (92.0)	
Invasive lobular	6 (8.2)	55 (8.0)	

Data are shown as median (minimum-maximum) or n (%). ER = Estrogen receptor, PR = progesterone receptor, CERB =HER 2 = human epidermal growth factor receptor 2.

breast carcinoma are present in approximately 10% of patients at the time of diagnosis, while 30% of patients develop metastatic disease during and after treatment [3-5]. Although breast cancer can metastasise to a wide variety of organs, the most common metastatic sites are bone, lung, liver and skin. In addition, more and more types of breast cancer metastatic sites are reported in the literature. For these uncommon metastatic sites, there are publications that define "unusual metastasis", which is a definition that defines a frequency of ≤ 1% in each site, and according to this definition, unusual metastasis includes metastases involving the central nervous system, secretory / endocrine organs and glands, some internal organs and gynecological organs [6, 7].

Mediastinal lymph node involvement is a rare site of metastasis in breast cancer and mediastinal lymph node metastases are present in only 2% of patients with breast cancer [8]. Another risk of mediastinal lymph node involvement is that it may affect the oesophagus and there is a risk of spread of the existing involvement to the oesophagus. According to breast cancer autopsy reports, the prevalence of mediastinal metastases affecting the oesophagus is 0.4-6% [7, 8]. In our study, only 14 patients had mediastinal lymph node involvement among unusual metastasis localisations and the rate of mediastinal lymph node metastases among unusual metastases was 17.7%. In our analysis, there was no case with proven involvement of the oesophagus.

Involvement of the trachea and bronchial structures within the mediastinal structures is also rare and especially endobronchial metastasis is a very rare metastatic pattern in breast cancer [9]. In our study, one patient had a case involving the bronchial tree. Although lung metastases are common in breast cancer, pulmonary metastases with hilar masses as the primary finding are also rare in clinical practice and this involvement may present as spiculated masses with a picture including obstructive pneumonia and mediastinal lymphadenopathy [10]. In our study, hilar lymphadenopathy was present in four cases presenting with hilar lymphadenopathy, in other words, hilar lymphadenopathy was present in 5% of unusual metastases.

If we continue to look at mediastinal structures; secondary or metastatic tumours spread to the pericardium and heart more frequently than primary tumours. The most common causes of metastatic involvement are lung carcinomas, breast carcinomas, haematological malignancies and gastrointestinal carcinomas. Metastatic involvement of the heart and pericardium is usually associated with a very poor prognosis and most cases are clinically silent and not diagnosed in vivo until autopsy [11, 12]. In our study, we had one patient with metastases invading the mediastinum and spreading to the pericardium and right atrium.

Breast cancers are among the most common tumours metastasising to the head and neck, and metastases have been reported in almost every anatomical subregion of the head and neck. However, cervical metastases of breast carcinoma are still relatively rare in clinical practice, as the presence of metastases to the head and neck is rare in cancer practice [2]. The most frequently involved tissue in the head and neck region is the cervical lymph nodes and its incidence is as low as 1% [13, 14]. In our study, we found the rate of cervical lymph node metastasis among unusual metastases to be 11.3% (n = 9). The thyroid gland and salivary glands are the most rarely reported metastatic sites in the head and neck region. In our retrospective analysis, we did not detect any metastasis to the thyroid gland, but we found metastasis to the parotid gland in only one case (Fig. 1a). The parotid gland is the salivary gland with the most frequent metastatic involvement among other salivary glands. The most common malignancies that metastasise to the parotid gland are tumours originating from the head and neck, such as squamous cell carcinoma and malignant melanoma, and in fact breast cancer is among the malignancies that rarely metastasise to the parotid gland and also has a poor prognosis. To give a statistic, only 21 cases have been reported from 1982 to 2017 [15, 16]. Again anatomically, orbit is one of the rare metastatic localisations in the head and neck region. Orbital metastases from solid cancers are rare and constitute only 1-13% of orbital tumours. Breast cancer is responsible for 28-58.5% of these metastases. However, orbital involvement is exceptional in breast cancer, with only 0.7% of cases being symptomatic, and orbital metastasis is an important cause of morbidity that reduces patient quality of life [17].

Lacrimal gland tumours are also rare among or-

bital structures. The most common type of malignant lacrimal gland tumour is epithelial tumours, which are responsible for 58% of all malignant tumours in the lacrimal gland. Metastasis to the lacrimal gland is extremely rare and only sporadic cases have been previously reported [18]. In our case, cancer metastasised to the soft tissues including the upper eyelid and lacrimal gland (Fig. 1b).

The oral cavity is also an anatomical region that is rarely metastatically involved, accounting for less than 1% of all malignant neoplasms. Metastasis of breast cancer to the oral cavity is relatively less common, with 85% of metastatic tumours in the oral cavity occurring most commonly in the jaw bones, particularly the mandible in 80-90% of cases. Metastasis to the soft tissues of the oral cavity is extremely rare, accounting for approximately 0.1% of all oral malignancies. The most commonly involved metastatic sites are the tongue, gingiva and lips; less frequently involved sites are the palatal and buccal mucosa, respectively [19]. In our single case, there was a metastatic focus involving the mandibular ramus, extending the bone and invading the adjacent soft tissue (Fig. 1c).

Although the tendency of breast cancer to spread to the central nervous system is well known, the prevalence of symptomatic central nervous system metastases in breast cancer ranges from 5% to 16%, Brain metastases are an important source of morbidity and mortality in breast cancer patients as in other types of cancer. Metastatic breast cancer has become the second most common cancer causing brain metastases after lung cancer [20]. The blood-brain barrier plays a critical role in maintaining normal brain function. The blood-brain barrier, the biological structure between blood and brain parenchyma, separates the blood compartment from the brain tissue, restricting the entry of toxic molecules and protecting the parenchyma by expelling metabolites and waste products. This barrier is also one of the main barriers for extravasation and colonisation of cancer cells into the brain. However, with the development of primary or metastatic tumours in the brain, significant changes occur in this context: During tumour evolution, the blood-brain barrier is disrupted with new anarchic vascularisation and tumour cells are likely to cross the barrier [21-23].
Spinal cord metastasis as a component of the central nervous system is even rarer. The mechanism of intramedullary dissemination has not been well established. Possible routes of transmission may be lymphatic or haematological transmission, direct spread from the vertebrae or descending from the brain. In our study, there was no case with spinal cord involvement. Metastasis to the leptomeninges, another component of the central nervous system, is also rare and studies have reported the predisposition of the lobular histopathological subtype to leptomeningeal carcinomatosis [2, 24]. In our study, leptomeningeal involvement was present in 2 cases and both of them were lobular type invasive carcinoma in accordance with the literature.

Breast cancer is known to metastasise to all organs of the body. However, abdominal lymph node metastases from breast cancer are extremely rare. The mechanism of abdominal lymph node metastases from breast cancer is still unclear. Studies have shown that the metastatic patterns of breast cancer depend on the pathological type and the rate of metastatic spread to the gastrointestinal tract is higher in invasive lobular cancer type than in invasive ductal cancer type and this molecular subtype may be a determinant in metastasis preference. Based on these data, although abdominal lymph node metastasis from invasive ductal type breast cancer is rare [25], the rate of mesenteric lymph node involvement among unusual metastases was 11.3% (n = 9) and 6 of these patients had mixed pattern and 3 had invasive ductal carcinoma histopathological subtype.

As mentioned above, gastrointestinal system metastases in breast cancer are also rare and unique and the incidence in autopsy series varies between 8% and 35%. Any part of the gastrointestinal tract from the tongue to the anus may be involved. In most series, lobular carcinoma has been reported to have a higher tendency to metastasise to the gastrointestinal tract and peritoneum, but the data on this tendency are not conclusive. In a large review, the most common site of gastrointestinal tract metastasis was the stomach with 185 cases, while colon involvement was reported in 59 cases and small bowel involvement in 24 cases [2]. Although the stomach is the most common site of breast cancer metastasis, the incidence is quite low, approximately 0.2%-0.7% [26]. Colon metastases are even rarer and often pose a diagnostic dilemma and are difficult to diagnose due to their non-specific pres-

entation and similarity to other malignant or benign lesions [27]. In our breast cancer cohort, only one of the 79 patients with unusual metastases had a gastrointestinal system component, which was localised in the colon, and the patient had only nonspecific abdominal pain.

Adrenal metastases are the most common malignancy in the adrenal glands, another anatomical localisation where metastases are much less common. In order of frequency, the main cancer types metastasising to the adrenal gland are lung cancer, gastric and colon cancer, oesophageal cancer, liver/ biliary tract cancer and renal cell carcinoma. The symptoms of adrenal gland metastasis are almost always asymptomatic. However, if a large part of the adrenal cortex is damaged by a tumour or if both adrenal glands are affected, they may be associated with signs and symptoms of adrenal insufficiency [28]. The presence of adrenal metastases in breast cancer is very rare and some publications have stated that adrenal gland metastases in invasive ductal carcinoma represent an extremely low number of cases [29]. However, in our retrospective analysis, 5 of 79 unusual metastasis localisations had adrenal metastases. Contrary to the literature, none of the adrenal metastases had lobular subtype and four cases had invasive ductal carcinoma histopathological subtype and only one case was solid papillary carcinoma with neuroendocrine differentiation (Fig. 1d).

Among the anatomical sites of visceral metastasis of breast cancer, kidney, spleen and pancreas are also metastatic sites that have been reported rarely. Spleen metastasis is rarely seen as a single site without a component of other metastatic foci and this condition is very rarely reported in the literature. In a recent publication on this subject, it is mentioned that solitary spleen involvement was detected in only three cases before them [30]. In our study, two cases had splenic metastases and they were not solitary but were components of multiple foci seen in other regions. When we look at the metastases of breast cancer to the pancreas, although the prevalence of pancreatic metastases was reported to be as high as 11% in a large autopsy series, resection of pancreatic metastases from breast cancer is extremely rare and only 20 cases have been reported so far in a recent study [31]. In our study, one patient had a metastatic mass localised in the tail of the pancreas (Fig. 1e).

In rare cases, breast cancer metastases can also involve the genital organs and placenta. Symptomatic cases of uterine metastases may present as vaginal bleeding or abdominal discomfort, but most cases are diagnosed post-mortem. Studies have shown that the incidence of ovarian metastases in breast cancer patients is 13-47%, based on autopsy series. Ovarian metastases usually present as an asymptomatic ovarian mass. Metastatic lesions are known to reach the genital organs via lymphatic and blood vessels or transcoelomic spread through the peritoneal cavity, thus forming metastatic foci [2, 32]. In our cases, uterus and ovary were involved together in 2 cases, while 2 cases had metastatic foci in the ovary.

Since approximately 65-75% of patients with metastatic disease from breast cancer have bone metastases, we can talk about 'relatively rare bone metastases' in the case of breast cancer. The pattern of occurrence of atypical bone metastases and the presence of other bones with concomitant involvement also affect this 'relative rarity'. Breast cancer metastases most commonly affect the spine, ribs and pelvic bones; however, only 3.5% of breast cancer patients develop long bone metastases [33, 34]. In two of our cases, only femur was involved among the bone structures. In the category of bone metastases, skull metastases are malignant bone tumours with an increasing incidence. Cranium involvement has been reported in lung, breast and thyroid carcinoma, renal cell carcinoma, malignant melanoma in adults and neuroblastoma in children. In four of our cases, only the cranium was involved, while in one case the cranium and humerus were involved together. The occurrence of the sternum as a focus of bone metastasis in breast cancer patients is relatively rare and the reported incidences are 1.9%-5.2%, respectively [35-37]. We had metastasis to the sternum in one of our cases. One of the other involvements, which can be considered as our relatively rare metastasis experience, was isolated pelvis and isolated scapula involvement (Fig. 1f).

Breast cancer is a heterogeneous group of tumours with variable morphology, behaviour, response to treatment and molecular profiles. Invasive ductal carcinoma is the most common histological type accounting for 72-80% of all invasive breast cancers, while invasive lobular carcinoma is less common and ac-

counts for 5-15% of all invasive breast cancers. These two subgroups differ from each other in many aspects such as risk factors, histological features and molecular profile. The metastatic site tropism of these two subgroups is also different from each other. Metastatic pattern analysis studies in breast cancer have shown that lobular tumours have a higher tendency to metastasise to the peritoneum, adrenal glands, uterus and pleural surface. We discussed the histopathological subtype relationships of the unusual metastases we detected above in the text. In some respects, our study is consistent with previous studies in terms of histopathological subtype/unusual metastasis localisations, while in some cases we found different data from previous studies. Molecular profiling studies, as well as histopathological subtype, are another important issue discussed in the context of cancer and its preferred metastatic foci [38-41]. Since the number of 79 unusual metastasis localisations we detected in our retrospective analysis of our large cohort of 852 cases was insufficient on a group basis (some groups had one patient), we compared invasive ductal carcinoma and lobular carcinoma histological subtypes in terms of the presence of unusual metastasis without dividing the patients into groups, but we did not find a statistically significant difference between them. We then divided the patients into four different receptor subgroups and analysed the difference between receptor groups and the presence of unusual metastasis; however, we did not find a statistically significant relationship between receptor groups and the presence of unusual metastasis (Table 2).

Limitations

The limitations of this study are the small sample size and the single centre of the study.

CONCLUSION

Despite all the latest technological advances in the diagnosis and treatment of breast cancer, most deaths from cancer are caused by metastases that are unresponsive to conventional therapies. Scientifically, all studies that will enable us to understand the process of metastatic development at the cellular and molecular level have the potential to serve very important studies for the improvement and development of effective treatments for cancer. In clinical practice, timely diagnosis of unusual metastases provides an important chance to control the disease and prolong survival. When past studies are reviewed, we come face to face with the fact that the rates of unusual metastases detected in autopsy cases are much higher and that some symptoms and metastatic foci of patients are missed in practice. In this study, we wanted to contribute to the awareness of unusual metastases of breast cancer by sharing the archive of our hospital, which is an important oncology centre in Turkey, through our cases.

Authors' Contribution

Study Conception: PÖA, NÇ; Study Design: PÖA; Supervision: PÖA, NÇ; Funding: N/A; Materials: PÖA; Data Collection and/or Processing: PÖA; Statistical Analysis and/or Data Interpretation: PÖA, NÇ; Literature Review: PÖA; Manuscript Preparation: PÖA and Critical Review: PÖA.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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