Idiopathic and Radiation-Induced Myxofibrosarcoma In Head And Neck-Case Report And Literature Review

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Case report

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Abstract

Background

Myxofibrosarcoma (MFS) is a rare malignant fibroblastic tumor that primarily occurred in proximal extremities of older people. However, MFS, especially radiation-induced MFS is extremely rare in the head and neck. Local recurrence is very common, the diagnosis and treatment of MFS is always a great challenge. We presented one case of radiation-induced MFS, combined with previous literature, the clinical features, essentials of diagnosis and treatment modalities of MFS in head and neck were reviewed to better understand this rare entity.

Case presentation

Here, we reported a case of radiation-induced MFS under left occipital scalp in a 20-year-old girl with a history of medulloblastoma surgery and radiotherapy in 2006. A total tumor resection was performed with preservation of the overlying scalp the underlying bone, and no adjuvant therapy was administered after surgery. Post-operative pathological diagnosis was high-grade MFS. Unfortunately, the tumor relapsed six month later. Then a planned extensive resection was carried out, followed by radiotherapy. In addition, intra-operative frozen section was sent to confirm negative surgical margin. No relapse occurred in 12-month postoperative follow-up.

Conclusions

Planned gross total resection (GTR) with negative margins is the reasonable choice and footstone of other treatments for MFS. Ill-defined infiltrated borders and the complicated structures make it a great trouble to achieve total resection of MFS in the head and neck. Therefore, adjuvant radiotherapy and chemotherapy seem more necessary for these lesions. Further studies are needed to confirm the efficacy of radio-chemotherapy for head and neck MFS.

Background

Myxofibrosarcoma (MFS) is a rare soft tissue sarcoma that can arise sporadically or be induced by radiation, representing approximately 5% of all sarcomas. MFS is one of the common soft tissue tumors in the extremities of elderly patients, It can also be located on the trunk (12%), retroperitoneum or mediastinum (8%). However, MFS, especially radiation-induced MFS in the head and neck is extremely rare.

MFS normally appears as painless and slow-growing dermal or subcutaneous masses. Clinically, it is characterized by tumor progression with increased metastases after local recurrences. MRI is the most common pre-operative diagnostic modality. Histological grading of primary MFS was determined according to the updated French Federation of Cancer Centers (FNCLCC) scheme. Due to the high rate of recurrence, planned, gross total resection (GTR) with clear margins is essential and adjuvant treatment involving radiotherapy and chemotherapy is advised. However, due to ill-defined infiltrated borders and complex anatomical structures in the head and neck region it is technically harder to achieve gross total resection. Therefore, radiotherapy as well as chemotherapy looks more necessary for MFS in head and neck than in the extremity.

To the best of our knowledge, only 28 cases have been reported in the head and neck so far, 3 of them was induced by radiation (Table 1). Our case is the first case of scalp MFS following radiation exposure in a young female. Given its relatively recent recognition and the low incidence, only single cases or very small series have been reported, there are no randomized trials to guide treatment protocols. Without standard treatment protocols, it appears challenging to precisely predict prognosis for primary MFS by evaluating clinicopathological factors. Herein, we reported a case of radiation-induced scalp MFS in a 20-year-old girl with a history of medulloblastoma surgery and radiotherapy in 2006. Based on case report and literature review, we discussed clinical, histopathological features, treatment strategies and prognostic factors of MFS in the head and neck, in order to contribute to a better understanding of this potentially fatal malignancy.
| Case Number | Author/Year                  | Sex/Age (Year) | Radiation-Induced (YES/NO) | Location          | Image     | Biopsy (YES/NO) | Treatment | Tumor Margin | LR (YES/NO) | Metastasis (YES/NO) | Follow-Up (Month) |
|-------------|------------------------------|----------------|---------------------------|-------------------|-----------|----------------|-----------|--------------|-------------|----------------------|--------------------|
| 1           | Lam PK et al., 2002          | M/55 NO        | Sphenoid Sinus            | CT, MRI           | YES       | S              | NE        | NO           | NO          | NO                   | 8                  |
| 2           | Udaka T et al., 2002         | M/55 NO        | Neck                      | CT, MRI           | NO        | S              | NE        | NO           | NO          | NO                   | 27                 |
| 3           | Nishimura G et al., 2006     | M/69 NO        | Hypopharynx               | CT, MRI           | YES       | S              | PO        | NO           | NO          | NO                   | 16                 |
| 4           | Kuo J et al., 2007           | M/28 YES       | Brain                     | CT, MRI           | NO        | S + RT         | N/A       | N/A          | N/A         | N/A                  | N/A                |
| 5           | Wang M et al., 2008          | F/63 NO        | Orbit                     | CT, MRI           | NO        | S              | PO        | YES          | NO          | 2                   |
| 6           | Enomoto K et al., 2008       | M/68 YES       | Sphenoid Sinus            | CT, PET           | N/A       | N/A            | N/A       | N/A          | N/A         | N/A                  | N/A                |
| 7           | Gugatschka M et al., 2010    | M/79 NO        | Hypopharynx               | Endoscopy CT      | NO        | S              | NE        | NO           | NO          | N/A                  |
| 8           | Li X et al., 2010            | F/37 NO        | Parotid                   | CT                | NO        | S + RT         | NE        | NO           | NO          | 8                   |
| 9           | Buccoliero AM et al., 2011   | M/9 NO         | Brain                     | CT, MRI           | NO        | S + RT + C     | PO        | YES          | NO          | 15                  |
| 10          | Srinivasan B et al., 2011    | F/78 NO        | Parotid                   | MRI               | YES       | S + RT + C     | NE        | NO           | NO          | 18                  |
| 11          | Norval EJG et al., 2011      | M/69 NO        | Maxillary Sinus           | CT, MRI           | YES       | RT + C         | N/A       | N/A          | N/A         | 12                  |
| 12          | Gire J et al., 2011          | M/17 NO        | Orbit                     | CT, MRI           | NO        | S              | PO        | NO           | NO          | 24                  |
| 13          | Qiubei Z et al., 2012        | M/42 NO        | Hypopharynx               | CT                | YES       | S              | NE        | NO           | NO          | 36                  |
| 14          | Nakahara S et al., 2012      | M/52 NO        | Maxillary Sinus           | MRI, Fdg-PET     | YES       | S + RT         | NE        | NO           | NO          | 17                  |
| 15          | Wemhart S et al., 2013       | M/73 NO        | Brain                     | MRI               | NO        | S + RT + C     | N/A       | N/A          | YES         | 2                   |
| 16          | Cante D et al., 2013         | M/66 NO        | Maxillary Sinus           | CT, MRI           | YES       | RT + C         | N/A       | N/A          | YES         | 18                  |
| 17          | Majumdar K et al., 2013      | F/21 NO        | Brain                     | CT, MRI           | NO        | S + RT         | PO        | YES          | NO          | 30                  |
| 18          | Darouassi Y et al., 2014     | F/74 NO        | Thyroid                   | CT                | NO        | S + RT + C     | N/A       | YES          | NO          | N/A                  |
| 19          | Dell'Aversana OG et al., 2014| M/35 NO        | Maxillary Sinus           | CT, MRI           | YES       | RT             | N/A       | NO           | NO          | 27                  |
| 20          | Shimoda H et al., 2016       | M/67 NO        | Pterygopalatine Fossa     | CT                | YES       | S + RT         | PO        | YES          | NO          | 32                  |
| 21          | Costa DA et al., 2016        | M/10 NO        | Brain                     | CT, MRI           | N/A       | S + RT         | PO        | YES          | YES         | N/A                  |

Abbreviations: C, chemotherapy; F, female; LR, local recurrence; M, male; NE, negative; PO, positive; RT, radiotherapy; S, surgery.
Tumors in the extremities usually present as a slowly enlarging, painless mass which can be located subcutaneously, presenting as a multinodular form, or appears to be the most frequent site, especially the maxillary sinus, followed by brain. Similar to MFS in other regions, MFS in the head and neck mainly affects the older male patients (M/F = 19:11), although the age range is broad, most patients are in their fifth to seventh decades of life, with a mean age of 40.9 years. However, the onset age of radiation-induced myxoblastoma seems to be associated with the time of receiving radiotherapy.

Given the use of modern methods including immunohistochemistry and molecular studies, MFS was proved to be not of true histiocytic origin and the high-grade end of MFS was considered as a part of the myxoid variant of Malignant fibrous histiocytoma (MFH). It was until late 1990s that the poorly recognized low-grade variant was construed as a part of the morphological continuum of MFS by Mentzel et al. Given the use of modern methods including immunohistochemistry and molecular studies, MFS was proved to be not of true histiocytic origin but of fibroblastic origin. MFS was defined as a distinct type of fibroblastic sarcoma by the WHO in 2002, and MFH was renamed undifferentiated pleomorphic sarcoma.

MFS usually develops in proximal extremities of older people with a mean age of 65 years, men are usually affected slightly more often than women. MFS in the head and neck is extremely rare, representing approximately 3% of MFS. To the best of our knowledge, only 28 cases have been previously elaborately described in the head and neck regions so far, including brain (5, 17.9%), maxillary sinus (5, 17.9%), scalp (4, 14.2%), orbit (3, 10.7%), hypopharynx (3, 10.7%), sphenoid sinus (2, 7.2%), parotid (2, 7.2%), infratemporal space (2, 7.2%), thyroid gland (1, 3.5%), and multiple lesions (1, 3.5%) (Table 1). Paranasal sinus appears to be the most frequent site, especially the maxillary sinus, followed by brain. Similar to MFS in other regions, MFS in the head and neck mainly affects the older male patients (M/F = 19:11). Although the age range is broad, most patients are in their fifth to seventh decades of life, with a mean age of 40.9 years. However, the onset age of radiation-induced myxofibrosarcoma seem to be associated with the time of receiving radiotherapy.

Tumors in the extremities usually present as a slowly enlarging, painless mass which can be located subcutaneously, presenting as a multinodular form, or deeply as a single mass between the muscle masses underneath the superficial fascia. Because of the complexity of the anatomical structure of the head...
and neck, MFS in this region illustrates a wide variety of presentations of primary tumor ranging from an exophytic mass to subcutaneous nodules within the paranasal sinus, infratemporal fossa, pterygopalatine fossa, or intracranial, so it can cause focal neurological deficit and symptoms of intracranial hypertension, such as headache and vomiting, focal neurological deficits.\textsuperscript{5–30} In our case, the tumor presented as rapidly progressive enlarging, painless mass, which was a superficial type and didn't infiltrate the skull. Clinically, MFS is characterized by its unusual infiltrative growth pattern, significant propensity for local recurrence and tumor progression with increased metastases after relentless local recurrences. Mentzel et al. classified MFS into superficial and deep groups.\textsuperscript{1}

Radiation-induced sarcomas (RIS) are increasingly seen in long-term survivors of head and neck cancers, with an estimated risk of up to 0.3%. Common histologic subtypes of RIS parallel their idiopathic counterparts and mainly include osteosarcoma, chondrosarcoma, malignant fibrous histiocytoma and fibrosarcoma.\textsuperscript{34} Radiation-induced MFS is very rare, only 3 cases were reported until now. The diagnosis of RIS requires the following criteria: \textsuperscript{35} (1) history of radiotherapy; (2) asymptomatic latency period of several years (conventionally, > 4 years); (3) occurrence of sarcoma within a previously irradiated field; and (4) histological confirmation of the sarcomatous nature of the post-irradiated lesion. In our patient, the secondary myxofibrosarcoma met all the criteria for a RIS, including development of myxofibrosarcoma within the radiation field, 11 years’ latent period, and a different histopathological type.

MRI is the most common diagnostic modality. Computed tomography (CT) is also effective in soft tissue tumor diagnosis, especially for those located near the presence of air and bone. MFS has low attenuation on CT and shows low-to-intermediate signal on T1-weighted MRI. The solid and myxomatous components both show high signal on T2-weighted MRI. MFS often show abnormal signal infiltration along the facial plan on MRI that correspond to an infiltrative growth pattern histologically, named "tail sign". Post-contrast images can better display tail sign than T2-weighted image.\textsuperscript{36,37} Thus, in order to define the boundaries of the tumor before operation, it is critical that patients presenting with a diagnosis of MFS undergo high-quality T1- and T2-weighted MRI with pre-and post-gadolinium imaging. However, due to lack of typical MRI features, it is always a great challenge to differentiate MFS from other tumors in the head and neck.

The definitive diagnosis of MFS depends on pathological examination. Histologically, in order to diagnose MFS, a series of general parameters must be present like spindled shaped cells, elongated, pleomorphic nuclei, abundance of curvilinear vessels with thin walls and myxoid matrix.\textsuperscript{38} Low-grade tumors are associated with small amount of myxoid tissue, low mitotic activity and no necrosis; while high-grade tumors present with large population of cells, less myxoid matrix, multinucleated giant cells, increased mitotic index and important areas of necrotic tissue. The intermediate-grade tumors lend particularities of the other two but in smaller amount, without well-developed solid and necrotic areas or significant pleomorphic cells.\textsuperscript{38,39}

Currently, no specific immunohistochemical markers are available to definitely diagnose MFS. However, positive for vimentin and, some-times positive for CD-34 and negative for S-100 protein. muscle-specific actin, desmin, myogenin can support the diagnosis. Ki-67 is able to reflect tumor aggression when it is intensely expressed, while high expression of minichromosome maintenance protein 2 may be correlated with a short period until first recurrence.\textsuperscript{39}

Similar to other sarcomas, GTR (including nerves, vessels, and any involved bone) with negative margins remains the primary treatment for MFS.\textsuperscript{40} In order to fulfill a total resection, a planned operation based on biopsy and a high-quality MRI imaging are necessary. Biopsy is necessary to orientate the diagnosis or even establish the type of soft tissue sarcoma. Unfortunately, in many cases, the actual tumor boundary was usually underestimated on MRI sequences due to infiltrative grown along the facial planes. Thus, an extended resection is necessary for these individuals, while the extent of the resection is controversial, various surgical margins from 1cm to 5 cm were reported previously.\textsuperscript{40–48} In order to confirm that the surgical margin was microscopically free of tumor, frozen section in operation and postoperative histological assessment are recommended. In MFS patients who undergo primary unplanned resection and are thus at high risk of local recurrence, it is thought necessary to consider additional resections. Merck et al. reported that if non-radical excisions preceded a radical resection, the local failure rate was up to 33%, in comparison to 17% for primary wide resection because of the unusual infiltrative growth of MFS.\textsuperscript{49} However, it is more technically difficult to achieve radical resection in the head and neck region, especially in the deep area, for example tumors in paranasal sinus, orbit, and intracranial where vital structures can limit the extent of resection. In the reviewed 28 cases, only 7 cases were reported to be totally resected and free of tumor in the margin (Table 1). The total resection rate is far more lower than other part of the body. For these patients it is necessary to consider additional therapeutic approaches such as radiotherapy or chemotherapy. Based on randomized trials including a multitude of sarcoma subtypes, radiotherapy can significantly reduce local recurrence.\textsuperscript{50} Unfortunately, the role of adjuvant radiotherapy and chemotherapy in the treatment of MFS is less clear due to the rarity of this tumor. Only several small studies reported the efficacy of chemotherapy in myxofibrosarcoma.\textsuperscript{51,52} Additionally, RIS is always insensitive to radiotherapy since they are induced by radiation. Therefore, the impact of radiotherapy and chemotherapy on relapse-free survival of MFS patients remains to be proven.

MFS is a locally aggressive tumor that have a propensity for local recurrence (LR), even after complete resection, the risk of recurrence is high, ranging from 16–57% (Table 2), usually associated with histologically higher grade, thereby conferring a metastatic propensity. In contrast, the metastatic rate of MFS is low, between 20% and 25%, the most common site is the lung, followed by the pleura, lymph nodes and bones.\textsuperscript{40–48} LR is more common for MFS in the head and neck region. In the reviewed 28 cases, LR rate was 43% (9/21), all the RIS cases developed tumor relapse. But only 6 (25%, 6/24) cases developed tumor metastasis. Additionally, The prognosis of patients with RIS is generally is generally worse than that with primary sarcomas of a similar stage.\textsuperscript{34} Up to now, the prognostic parameters for MFS are still controversial, previous studies provided inconsistent or even contradictory conclusions. The reasons for these variances among previous series were mostly attributed to varying diagnostic and grading criteria, lacks of critical evaluation of margins and appropriate multivariate survival analyses, small sample size and obscure definition of wide resection, which precluded drawing firm conclusions by meaningful comparisons. Despite controversies, in most studies, margin status is the most important predictor of LR, negative margin and wide resection is positively related to low LR.\textsuperscript{40–48} Therefore, margin-negative surgical resection is the cornerstone of treatment for MFS. Unfortunately, it is really a great challenge to obtain radical resection for MFS in head and neck region especially in the deep areas. There is a lot of things to learn about surgical technique and effects of adjuvant therapy on MFS.
Table 2

| Author/Year                  | No. Of Cases | Sex (M/F) | Age (Year) | Treatment (No.) | Tumor Margin Status (No.) | LR (%) | Metastasis (%) |
|------------------------------|--------------|-----------|------------|-----------------|---------------------------|--------|----------------|
| Ghazala CG et al., 2016⁵³    | 50           | 35/15     | 68.4 (median) | 49 | 37 | 21 | 28 | 14 | 28 |
| Daniels J et al., 2014⁴⁰     | 30           | 13/17     | 65.8 (mean)  | 30 | 23 | N/A | N/A | 26.7 | 5 |
| Look Hong NJ et al., 2013⁴¹  | 69           | 38/31     | 62 (median)  | 69 | 53 | 14 | 55 | 16 | 16 |
| Riouallon G et al., 2013⁴²   | 21           | 10/11     | 67 (mean)    | 21 | 21 | 17 | 4  | 57 | 9.5 |
| Kikuta K et al., 2013⁴³      | 100          | 61/39     | 64 (mean)    | 100 | 16 | 28 | 72 | 21 | 11 |
| Dewan V et al., 2012⁴⁴      | 172          | N/A       | 67 (mean)    | 166 | N/A | 45 | 127 | 17 | 20 |
| Haglund KE et al., 2012⁴⁵    | 36           | 21/15     | 72.5 (median) | 36 | 28 | 9 | 27 | 31 | 17 |
| Sanfilippo R et al., 2011⁴⁶ | 158          | 89/69     | 64 (mean)    | 158 | 81 | 28 | 130 | 18.2 | 14.6 |
| Lin C et al., 2006⁴⁷         | 70           | 38/32     | 64 (median)  | 61 | 28 | 26 | 43 | 44 | 23 |
| Huang H et al., 2004⁴⁸       | 49           | 26/23     | 60.5 (median) | 49 | 9  | 19 | 28 | 57 | 16.3 |
| Mentzel T et al., 1996¹      | 75           | N/A       | 66 (median)  | 74 | 13 | N/A | N/A | 54 | 22 |

Abbreviations: F, female; LR, local recurrence; M, male; NE, negative; PO, positive; RT, radiotherapy; S, surgery.

Conclusions

MFS are locally aggressive tumors that have a propensity for local recurrence. Effective education about MFS, high-quality MRI imaging, biopsy, correct early diagnosis, planned and wide surgical excision with safety margins are mandatory in order to provide the best results for the MFS patient. Unfortunately, the complex anatomical structure and the extent in mid cheek region, make MFS in the head and neck a hard “challenge” for the surgeon to obtain wide surgical margins of resection. Therefore, in order to avoid local and distant recurrences of MFS in this region, combined surgical and adjuvant chemoradiotherapy is absolutely recommended, although the role of chemoradiotherapy in the treatment of MFS is unclear and debated. Further randomized double-blind controlled clinical trials are needed to confirm the efficacy of combined chemoradiotherapy for MSF in head and neck.

Abbreviations

CT: Computed Tomography; GTR: Gross Total Resection; LR: Local Recurrence; MFS: Myxofibrosarcoma; MRI: Magnetic Resonance Imaging; RIS: Radiation-Induced Sarcoma; MFH: Malignant Fibrous Histiocytoma

Declarations

Authors' contributions

All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

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Not applicable.

Consent for publication

Written informed consent was obtained from the patients.

Competing interests

The authors declare that they have no competing interests
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Figures
Figure 1

T1-weighted image (A), T2-weighted image (B) and contrast-enhanced MRI scans (C) reveals a lesion with well-defined borders under the left occipital scalp. It exhibits hypointensity on the T1-W sequence image (A), slightly hyperintensity on the T2-W axial image (B) and mild peripheral enhancement after contrast administration (C). "Tail sign" is found on T2-W axial image (B, red arrows), and is more obvious in the Post-contrast images (C, red arrows); Intraoperative photographs show the skull was compressed and deformed by the tumor (E). The tumor is grayish and about 35×25 cm in size (F).
Figure 2

Histopathological examination. Hematoxylin and eosin [H&E] showing (A, ×100) alternating hypocellular (red arrow) and hypercellular (black arrow) areas, (B, ×200) spindle (red arrow) and stellate cells (black arrow), (C, ×200) tumor cells with pleomorphic (black arrow) and mitotic (thick black arrow) nuclei in the prominent myxoid matrix (red arrow); immunohistochemistry demonstrating positive staining for (D, ×200) vimentin and (E, ×200) SMA with a high (F, ×200) Ki-67 index (more than 50% of tumor cells).