Harlequin syndrome in a young patient with osteosarcoma after pleural metastasectomy: A case report and a mini review of the literature

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Abstract. Harlequin syndrome is a rare autonomic disorder with at least 83 reported cases in literature, 6% of which are congenital. When the fibers responsible for sudomotor and vasomotor supply to the face at the T2-T3 level are unilaterally blocked, it leads to hemifacial discoloration. This results in one-half of the face appearing flushed and hyperemic, sharply contrasting with the pale appearance of the other half. The cause of this syndrome is unknown; however, it appears to involve an autonomic nervous system dysfunction. It can be caused by an injury, compression, or blockade of sympathetic fibers along the pathway. The present study was a case of a metastatic osteosarcoma patient with a history of video-assisted thoracic surgery pleurectomy that presented in Attikon University Hospital (Athens, Greece) with worsening dyspnea and right-sided facial flushing.

Introduction

Harlequin syndrome (HS), initially reported by Lance *et al* in 1988, is a rare autonomic disorder caused by hemifacial cutaneous sympathetic denervation (1,2,3). It is characterized by semi-facial sweating and discoloration, sharply demarcated at the midline with normal ocular sympathetic innervation (3). It is mainly idiopathic in nature, often triggered by exercise, emotions or exposure to heat. HS is used to describe the transient hemi body flushing often observed in premature neonates due to immaturity of the hypothalamic centers and vasomotor instability (5). Congenital cases represent ~6% of all the patients with HS (3,6). However, it can also be a manifestation of underlying cervical and upper thoracic pathologies resulting in the compression of these sympathetic fibers or iatrogenic from the surgical or anesthetic procedures around the neck. The present study revealed, to the best of the authors' knowledge, the first case of an oncologic patient with HS as a result of pleural metastasectomy with video-assisted thoracic surgery (VATS).

Case report

A 28-year-old woman with a history of metastatic osteosarcoma was presented in Attikon University Hospital (Athens, Greece) with 5 days of worsening dyspnea, in September 2023. Computed tomography (CT) revealed new metastatic lung lesions. She had received neoadjuvant methotrexate, doxorubicin and cisplatin (MAP) (7) in October 2020 and undergone surgical removal of the tumoral mass of the right proximal humerus in February 2021. Histopathological examination from the lesion was suggestive of low-grade osteosarcoma (mdm2 amplified). Afterwards the female patient completed adjuvant treatment with MAP and Mifamurtide. In July 2022 contrast-enhanced CT thorax revealed new pleural nodules located mainly on left upper lobe. Pleural biopsy confirmed disease progression. After receiving three cycles of high dose ifosfamide (8) in September 2022, progression was reported with pleural metastatic lesions and clinical worsening. VATS metastasectomy was decided by the multidisciplinary team and the female patient underwent partial left pneumonectomy, pericardiectomy and pleurectomy in January 2023. The female patient was then enrolled in phase IV clinical trial and had already received three cycles of cabozatinib when presented in

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Attikon University Hospital (Athens, Greece) with new metastatic lung lesions and new onset dyspnea in September 2023.

Following emotional distress, on the third day of admission, the female patient presented with right-sided facial flushing and profuse sweating with the left side of the face remaining pale and dry (Fig. 1). The symptoms were resolved spontaneously after 15 min. The physical examination did not reveal any neurological alterations. No ophthalmological abnormalities were observed. Dermatological examination at rest revealed no abnormalities. Routine laboratory studies and carotid artery ultrasonography did not reveal any pathological findings. Pre-operative and post-operative contrast-enhanced CT images illustrated the anatomical region where the iatrogenic injury may have occurred and the diagnosis of iatrogenic HS was considered (Fig. 2A-C) (9). The patient succumbed after 2 days and did not experience any further episodes of Harlequin syndrome prior to their passing.

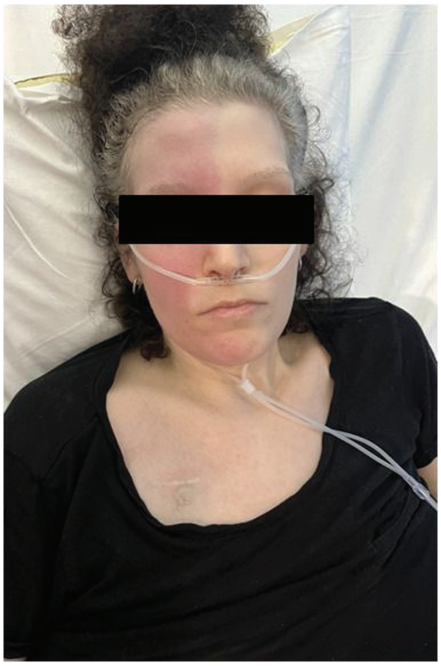

Figure 1. Right-sided facial flushing and profuse sweating with the left side of the face remaining pale and dry.

Discussion

The 28-year-old female patient represented an example of probable iatrogenic HS. Localization of the lesion in HS must be based on both the patient's clinical history and her constellation of symptoms.

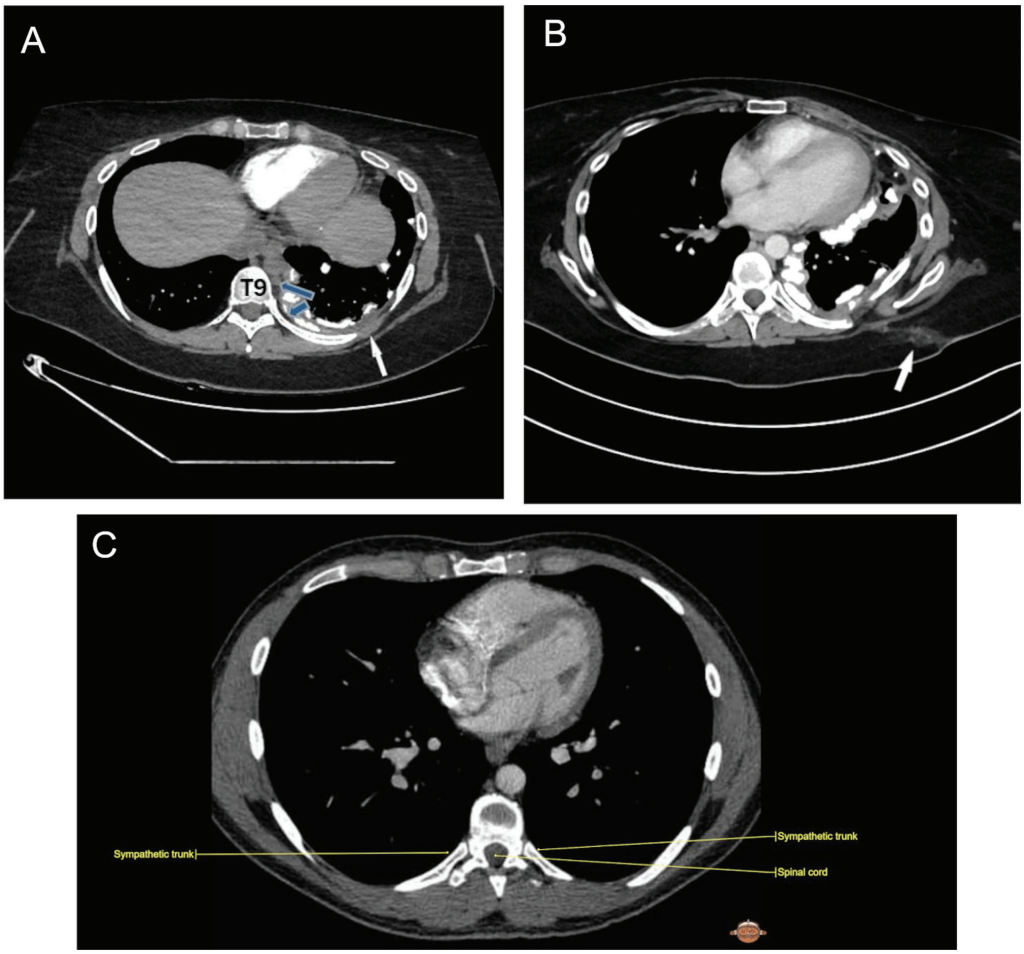

Figure 2. (A) Pre-operative contrast-enhanced CT image, axial section soft tissue window, demonstrates circumferential and nodular pleural thickening (white arrow) predominantly along the left lateral pleural space including mediastinum pleural surface along with extensive calcifications, representing osteosarcoma pleural metastasis; blue arrows reveal sympathetic chain. (B) Post-operative contrast-enhanced CT image, axial section soft tissue window, demonstrates post-operative changes in the subcutaneous fat of the left hemithorax (arrow) in 8th to 9th intercostal space. (C) Anatomic image of sympathetic track in 8th intercostal place; Courtesy of IMAIOS © 'Micheau A, Hoa D, e-Anatomy, www.imaios.com, DOI: 10.37019/e-anatomy'. CT, computed tomography.

Table I. HS case reports in PubMed database.

First author/s, year	Title	(Refs.)
Sharma *et al*, 2023	HS and autonomic seizures - a rare association	(25)
Navickaitė *et al*, 2023	Sarcoidosis-associated sensory ganglionopathy and HS: A case report	(26)
Karam *et al*, 2023	HS during peripheral cardiopulmonary bypass in a patient with an obstructing tracheal schwannoma: A case report	(27)
Melka *et al*, 2023	Idiopathic HS in a patient from Ethiopia: A case report	(28)
Giunta *et al*, 2023	Management of HS Under ECPELLA support: A report of two cases and a proposed approach	(29)
Hylton *et al*, 2022	HS as a complication of epidural anesthesia in an infant: Do adjunct medications play a role?	(30)
Dalldorf *et al*, 2022	HS following regional liposomal bupivacaine use in a partial sternectomy	(31)
Yan *et al*, 2022	HS induced by intraspinal analgesia in patients with advanced cancer: a case report	(32)
Korbi *et al*, 2022	Harlequin syndrome: An asymmetric face	(33)
Persson *et al*, 2022	HS associated with thoracic epidural anesthesia	(34)
Schultz *et al*, 2020	HS following microwave ablation in a child with a symptomatic paraspinal mass	(35)
Wagner *et al*, 2019	HS after thoracoscopic repair of a child with tracheoesophageal fistula	(12)
Tanaka *et al*, 2019	Cardiac sympathetic hyperactivity of lung cancer-associated HS	(36)
Elboukhar *et al*, 2019	Idiopathic HS: A case report and literature review	(37)
Pasrija *et al*, 2019	HS during venoarterial extracorporeal membrane oxygenation	(38)
Hans-Bittner *et al*, 2018	Do you know this syndrome? HS	(39)
Lee *et al*, 2017	HS and Horner syndrome after neck schwannoma excision in a pediatric patient	(40)
Lefevre *et al*, 2017	Development of HS following placement of thoracic epidural anesthesia in a pediatric patient undergoing Nuss procedure	(41)
Jeon *et al*, 2017	HS following resection of mediastinal ganglioneuroma	(42)
Algahtani *et al*, 2017	Idiopathic HS manifesting during exercise: A case report and review of the literature	(43)
Al Hanshi *et al*, 2017	A case study of HS in VA-ECMO	(44)
Kim *et al*, 2016	A pediatric case of idiopathic HS	(45)
Naqvi *et al*, 2016	HS with contralateral anhidrosis after an upper chest gunshot wound	(46)
Jung *et al*, 2015	Iatrogenic HS: A new case	(47)
Emsley *et al*, 2013	Post-exertional HS with spontaneous improvement	(48)
Breunig *et al*, 2012	HS in childhood - Case report	(49)
Pradeep *et al*, 2011	HS in a case of toxic goitre: A rare association	(50)
Moon *et al*, 2005	HS with crossed sympathetic deficit of the face and arm	(51)
Fallon *et al*, 2005	HS in two athletes	(52)
Lombardi *et al*, 2004	HS: An association with overlap parasomnia	(53)
Swan *et al*, 2003	Iatrogenic HS	(54)
Corbett *et al*, 1999	HS	(55)
Noda *et al*, 1991	HS due to superior mediastinal neurinoma	(56)
Lance *et al*, 1988	HS: The sudden onset of unilateral flushing and sweating	(3)

HS, harlequin syndrome.

The pathology can manifest at any point along the sympathetic outflow to the face. The second neuron (preganglionic fibers) leaves the spinal cord at T2-T3 and synapse with the third neuron (post-ganglionic fibers) in the superior cervical ganglion. Post-ganglionic fibers that supply the medial forehead and nose travel with the internal carotid artery, while fibers for other facial areas and the neck travel with the external carotid artery (10).

HS is caused by the unilateral blockade of the T2-T3 fibers carrying sudomotor and vasomotor supply to the face. VATS pleurectomy can rarely cause damage to the thoracic sympathetic chain (11). However, the possible mechanism of damage in the present case might be the utilization of diathermy or mechanical disruption (12). This method has been historically employed for treating palmar and axillary hyperhidrosis by interrupting the upper thoracic sympathetic chain (13).

Regarding causes of HS, ~54.6% of reported cases have idiopathic etiology, while in 45.4% of cases, the HS-associated symptomatology occurred secondarily, concurring with other autonomic nervous system impairments or iatrogenic (14). In adults, a majority of HS cases lack a discernible medical cause,

with one-third attributed to expanding neoplasms or iatrogenic damage (15).

The iatrogenic origin of HS has been documented in several cases. Fringeli *et al* (16) reported HS in a 55-year-old female patient with large median and right paramedian disc hernia-induced right C7 radiculopathy following C6-C7 fusion discectomy and additional anterior spondylodesis. Visible HS-suggestive symptoms on the right side of the face (flushing and excessive sweating), and contralateral facial anhidrosis, miosis and ptosis, were noted similar to the first case reported (3). Similarly, Sullivan *et al* (17) noted HS symptoms in a female patient post-T3 erector spinae plane block for radical mastectomy and axillary dissection, while Burlacu and Buggy described HS and Horner syndrome coexisting after left mastectomy and immediate latissimus dorsi reconstruction (18). Post-operative malignancies have also been linked to HS, such as in a case involving a 72-year-old man with squamous non-small cell lung cancer, where axillary and supraclavicular lymph node enlargement exerted compressive actions on nearby vascular structures, including carotid artery, the internal jugular vein and subclavian artery (19,20). Another possible iatrogenic cause of HS has been reported by Van Slycke *et al* (21) in a 74-year-old woman who underwent compressive retrosternal goiter thyroidectomy. Post-operation, patients reported recurring sudden left-sided facial flushing and sweating triggered by emotional changes, physical exertion, or heat. In some cases, HS could fully remit with no further relapses.

Treatment of HS typically depends on the severity of symptoms and the underlying cause. For most patients, HS is benign and does not require intervention. In cases where HS persists, treatment strategies are often tailored to the underlying condition or predisposing factor, especially if symptoms cause significant distress or social embarrassment. Stellate ganglion block (22), botulinum toxin injections to regulate sweating and other symptoms (23), surgery or radiation to remove a tumor or lesion (24) have been employed to manage symptoms of HS. The 28-year-old female patient of the present case report did not have oculomotor changes (ptosis or miosis), or upper extremity sudomotor or vasomotor changes. This indicates that T1 and T4 remained unaffected, thereby locating the sympathetic injury to the second or third thoracic segments of the spinal cord. Since this incident happened 8 months post left pleurectomy this indicates an iatrogenic HS. The present study reports, to the best of the authors' knowledge, the first case of a patient with HS as a result of pleural metastasectomy. HS case reports published in PubMed (https://pubmed.ncbi.nlm.nih.gov/) are summarized in Table I.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

MM and AK conceptualized the present study, performed the methodology, and wrote/prepared the original draft. AP, IK, PE, EE contributed to interpretation of the data. MK, AB, NG, EZ, KM contributed to acquisition of data. AP supervised the present study. AP, IK, PE, EE, MK, AB, NG, EZ and KM wrote, reviewed and edited the manuscript. All authors read and approved the final version of the manuscript. MM and AK confirm the authenticity of all the raw data.

Ethics approval and consent to participate

Written informed consent was obtained from the legal guardian for patient participation in the present study.

Patient consent for publication

Patient characteristics have been anonymized in compliance with ethical standards. Written informed consent was obtained from the next of kin for the publication of any associated images or patient data.

Competing interests

The authors declare that they have no competing interests.

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