ECRONICON OPEN ACCESS

EC PHARMACOLOGY AND TOXICOLOGY
Case Report

Heterotopic Peripheral Nerves Related to Sternal Abnormalities in Two Male B6C3F1 Mice

Klaus Weber*[1], Katrin Weber[2] and Edgar Weber[3]

[1]*AnaPath GmbH, Buchsweg 56, Oberbuchsiten, Switzerland*

[2]*AnaPath GmbH, Buchsweg 56, 4625 Oberbuchsiten, Switzerland*

[3]*Actelion Pharmaceuticals Ltd, Gewerbestrasse 16, 4123 Allschwil, Switzerland*

***Corresponding Author**: Klaus Weber, AnaPath GmbH, Buchsweg 56, Oberbuchsiten, Switzerland.

Received: March 22, 2017; **Published:** April 08, 2017

Abstract

In the sternum of two male B6C3F1 (SPF) mice used in a 104-week oncogenicity study, there was a developmental abnormality, not visible at necropsy. In one case, there was a large peripheral nerve of unknown origin located at a lateral parallel position to the normal appearing sternal segment. In the other case, there was a misshaped sternum with shorten segments and a cleft (sternoshisis). Within the cleft, a large nerve was present. It connected three large ganglia, each one was located within the cleft between each of the three segments.

Keywords: *Sternal Anomaly; Thoracic Wall Nerve Anomaly; Sternal Cleft*

Introduction

In the sternum of two male B6C3F1 (SPF) mice (Charles River, Sulzfeld, Germany) that were used in a 104-week oncogenicity study, there was an abnormality recorded that may be considered of a similar genesis for both cases.

Both, sternum and pectoral muscles originate from the lateral plate mesoderm [1,2]. The mesenchymal condensations are in contact at the rostral end of the thorax, at the site of the future manubrial condensation. Caudally to this point, the sternal bands are widely separated from each other [2].

In human, the earliest embryologic evidence of the sternum can be found at week 6 of gestation. The two lateral mesenchymal bands are not connected to ribs or each other. They fuse in the midline at a craniocaudal position to form the sternal body and the manubrium in week 10 [3].

During months 5 to 6 of development, chondrification is observed followed by ossification in single centers of the manubrium proceeding in ossification centers in a cephalocaudal direction in paired ossification centers in the sternal body [4].

In mice, cartilagineal precursor elements are noted from Theiler Stage (TS) 22/23 (days post coitem (dpc) 13.5-14.5) onwards. They fuse by TS 24 (dpc 15.5). Ossification centers are seen at dpc 17. At birth, the manubrium usually has a single ossification center. There are three 'square-shaped' sternebral ossification centers [1].

Due to the fact that in human the sternal development is completed with the first year after birth, it was deemed that most isolated sternal defects form from a failure of the mesenchymal lateral processes to fuse during the eighth week of gestation [3]. Any failure in the developmental process results in various sternal anomalies, such as fissure or foramen.

Material and Methods

In the sternum of two male B6C3F1 (SPF) mice (Charles River, Sulzfeld, Germany) that were used in a 104-week oncogenicity study,

there was an abnormality recorded that may be considered of a similar genesis for both cases. The lesions were not recorded during necropsy.

One of both males was a control group animal that was sacrificed at the terminal schedule on study day 728. There were no major gross lesions. The only significant lesion was a unilateral A-cell adenoma of the adrenal gland. There was no lesion in the skeletal system. The other male was a low dose group animal that was found dead on study day 652 during the course of the study. The most significant lesion was a hepatocellular adenoma that was considered to be the cause of the moribund conditions. There was no lesion in the skeletal system.

Histopathology was performed as a routine procedure in carcinogenicity studies performed at Harlan Laboratories Ltd, Switzerland in 2011, i.e., the animals underwent complete necropsies. Organs were sampled, fixed in formalin and subsequently trimmed, processed, embedded in paraffin wax, cut at an approximate thickness of 4 µm, and stained by hematoxylin and eosin. The sections were evaluated by light microscopy.

Results

In the terminally sacrificed control male, the sternum revealed histologically a normal appearance. The segment sampled at necropsy was lined by hyaline cartilage at both ends. The bone consisted of trabecular bone filled with active bone marrow. Lateral and parallel to the sternal bone segment, there was a large peripheral nerve of unknown origin (Figure 1). In this peripheral nerve tissue, there was a moderate multifocal axonal degeneration with related focal myelin sheet degeneration and Schwan cell activation present (Figure 2).

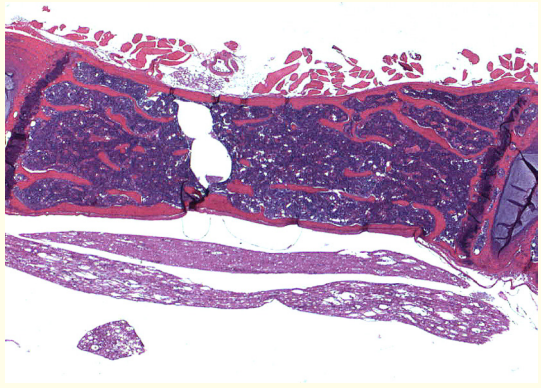

Figure 1: *Surviving mouse. Overview on normal shaped sternum with laterally located large diameter peripheral nerve of unknown origin (HE, lens x4).*

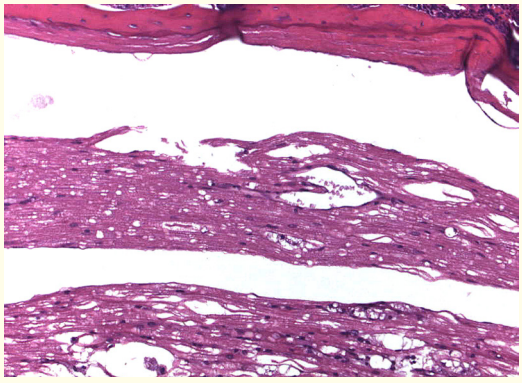

Figure 2: *Surviving mouse. Higher magnification. Nerve with multifocal, moderate axonal degeneration (HE, lens x20).*

In the male that died during the course of the study, the sternal segments were shorter than normal. Otherwise, the longitudinal half of the segments were developed in a normal way. The other half of three segments was separated by a cleft. These latter half segments were misshaped. The ends of the segment parts were indentured due to missing cartilage (Figure 3). There was a large nerve with three large ganglia present in the cleft. Each one of the ganglia was located within the cleft between each of the three segments (Figure 3). Also in this nerve, there were many foci of axonal degeneration. The ganglia were all located on the periphery of the large nerve, protruding towards the misshaped parts of the sternal segments. All ganglia consisted of large neurons surrounded with scattered satellite cells whereby the mass of neuronal cells formed a hilus (Figure 4).

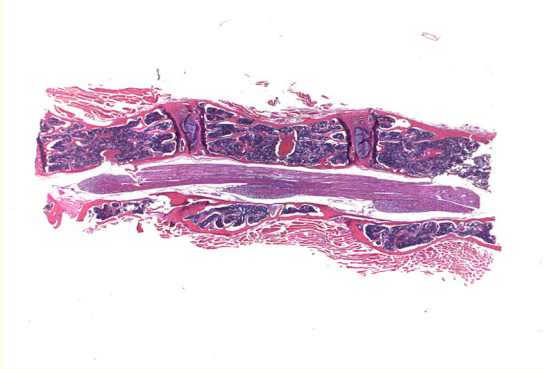

Figure 3: *Decedent mouse. Overview on the sternal segments shorter than normal. One longitudinal half of the segments are developed normal. The contralateral half of three segments is separated by a cleft. These half segments are misshaped with indentured ends. In the cleft, there is a large nerve with three large ganglia, each one is located in the cleft related to each of the three segments. The ganglia are located on the periphery of the large nerve, protruding towards the misshaped sternal segment parts (HE, lens x1.25).*

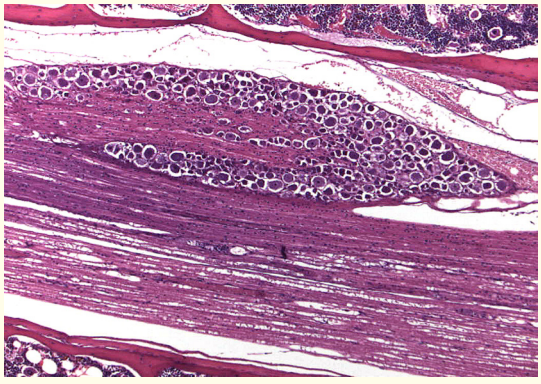

Figure 4: *Decedent mouse. Higher magnification of nerve and ganglion (HE, lens x10).*

Discussion

In a terminally sacrificed control male, the sternum revealed histologically a normal appearance. However, an unknown large diameter nerve was located in a lateral position in parallel to the sternal bone segments. An artefact by misplacement of peripheral nerve tissue could be excluded.

The largest nerve within the thoracic cavity is the phrenic nerve. It is however much smaller in diameter than the peripheral nerve recorded in both cases. The phrenic nerve is located close to the sternum, at the left and the right, within the mediastinum, running ven-

trally whereby crossing the lung hilus, and finally passing through the diaphragm. On the right, it follows the vena cava, and on the left, it crosses alone. No large diameter nerve is somewhere located close to the sternum. Nerves that are closed to the sternum consist only of small diameter sensible endings of the intercostal nerves. Therefore, the large nerve recorded at a lateral position to the sternum of one male is of unknown origin.

The second case differs by the location of a large diameter nerve within a sternal cleft or pseudocleft formation. Moreover, this nerve was connected with at least three ganglia, again located within the misshaped sternum. A cutting artefact could be excluded. To the author's knowledge, no similar case was published and even from sternal clefts or pseudoclefts, information on spontaneous cases in rodents are not available in the literature.

The etiology of sternal clefts is unknown. Some hypotheses include chronic nutritional deficiency, a lack of riboflavin during pregnancy, and disruption of the HoxB4 gene [4,5]. Furthermore, autosomal recessive prevalences [6] and sex-related predisposition [7] were also described in human.

Sternal clefts, also known as a bifid sternum or sternal fissure, is a partial or complete separation of the two lateral sternal bars [4]. Sternal cleft is a rare congenital defect of the anterior chest wall and is the result of a failed midline fusion of the sternum. There are complete and incomplete forms depending on the degree of separation. Three major categories of clefts are described in human: superior, inferior, and complete, whereby the superior cleft is the most common variant [5] and almost always an isolated abnormality [8]. In human, these defects are either U-shaped, ending at the level of the fourth costal cartilage or V-shaped with a cleft on the xiphoid process [9]. Published data on frequencies of main sternal variations and anomalies in human including suprasternal bone, suprasternal tubercle, complete manubriosternal fusion, complete sternoxiphoidal fusion, sternal foramen, sternal sclerotic bands, xiphoidal foramen, single foramen, single-ended or double-ended xiphoid process, and pseudocleft and pseudoforamen at the sternoxiphoidal junction amongst patients are available [10]. There is also a published overview on developmental disorders related to premature sternal fusion, manubrial segmentation, and multiple manubrial ossification centers in human patients [11]. The inferior clefts are most often associated with severe developmental defects, e.g., ectopia cordis [12].

Due to the fact that a nerve is involved in the present cases in mice, and both animals are from the same strain and the same breeder, and purchased at the same time point, it is considered that there is a relationship between both cases.

In the thoracic cavity, there is no large diameter peripheral nerve with ganglia present. Ganglia are connected to the spinal cord, the plexus or organs. Furthermore, all peripheral segmental nerves in the thoracic cavity provide sensible ramifications for the intercostal nerves that guide endings to the sternum. A possible source of the ganglia could be the cardiac plexus when considering ectopic lesions. However, the heart of the affected animal was devoid of any histological lesions. Furthermore, in the case of an affection of the cardiac plexus, it would be unlikely that three ganglia would be involved. In addition, nerves related to the cardiac plexus are much thinner. There is a suggestion published on the failure of the neural fold related to shortening of the body [13] that is associated with deformities of vertebrae, ribs and sternum. In such case, the sternum is broad and unsegmented or imperfectly segmented. However, there is no description available on ectopic nerves and ganglia.

Conclusion

In the sternum of two male B6C3F1 (SPF) mice used in a 104-week oncogenicity study, there was a developmental abnormality. Both cases are associated with an ectopic location of a peripheral large diameter nerve adjacent to or within the sternum. Due to the fact, that the animals are from the same strain, the same breeder and obtained at the same time point, a congenital syndrome may be assumed. No similar case was published as far.

Bibliography

1. Kaufman MH and Bard JBL. "The anatomical basis of mouse development". *Academic Press, San Diego, California* (1999): 58-59.

2. Mahone P., *et al*. "Prenatal ultrasonographic findings associated with wide clefting of the upper two thirds of the fetal sternum". *American Journal of Obstetrics and Gynecology* 166 (1992): 1219-1221.

3. Heron D., *et al*. "Sternal cleft: case report and review of a series". *American Journal of Medical Genetics* 59.2 (1995): 154-156.

4. Fokin A. "Cleft sternum and sternal foramen". *Chest Surgery Clinics of North America* 10.2 (2000): 261-276.

5. Mazzi JP., *et al*. "Superior sternal cleft associated with PHACES syndrome: postnatal sonographic findings". *Journal of Ultrasound in Medicine* 22.3 (2003): 315-319.

6. Haque KN. "Isolated asternia: an independent entity". *Clinical Genetics* 25.4 (1984): 362-365.

7. Gorlin RJ., *et al*. "Marked female predilection in some syndromes associated with facial hemangiomas". *American Journal of Medical Genetics* 52.2 (1994): 130-135.

8. Herman T and Siegel M. "Superior congenital sternal cleft". *Journal of Perinatology* 21 (2001): 334-335.

9. Firmin RK., *et al*. "Complete cleft sternum". *Thorax* 35.4 (1980): 303-306.

10. Yekeler E., *et al*. "Frequency of sternal variations and anomalies evaluated by MDCT". *American Journal of Roentgenology* 186.4 (2006): 956-960.

11. Lees RF and Caldicott JH. "Sternal anomalies and congenital heart disease". *American Journal of Roentgenology Radium Therapy and Nuclear Medicine* 124.3 (1975): 423-427.

12. Metry DW., *et al*. "The many faces of PHACE syndrome". *Journal of Pediatrics* 139.1 (2001): 117-123.

13. Grünenberg H. "The pathology of development. A study of inherited skeletal disorders in animals". *Blackwell Scientific Publications, Oxford* (1963): 154-155.

Volume 3 Issue 4 April 2017