Case Report

Bronchopleural fistula in a 5- years old child with novel CARMIL 2 mutation: A rare disease and a rare case

Ikram ul Haq Chaudhry *, Ahmed Alshaer, Burair Al Jassas, Amal Alkhunizi, Mohammad Alsaiary, Tasneem A. AlMubayaedh, Abass A. AlMalki, Ahmed Almesfer

Department of Pediatric Thoracic Surgery and Intensive Care Medicine, Infectious Disease, and Immunology, Maternity and Children Hospital, Dammam, Saudi Arabia

ARTICLE INFO

Keywords:
Genetic disease
CARMIL 2 mutation
Respiratory infection
Bronchopleural fistula
Surgery

ABSTRACT

A five year girl had eczema and allergic rhinitis in the past, presented with a history of cough, shortness of breath for the last one month. Her chest -X-ray showed a left side pleural effusion, and a computed tomographic scan (CT) of the chest showed left side hydropneumothorax. Left side 21 Fr drain was inserted. Her clinical condition deteriorated despite antimicrobial therapy, and she required mechanical ventilatory support due to respiratory distress. She also developed a right-sided pneumothorax that was managed by inserting a 21 Fr chest drain. A video-assisted thoracoscopic VATS procedure was done to staple the lung bullae and drain the empyema. Her post-operative chest X-ray showed good lung expansion. Pleural fluid culture report was positive for candida. She was commenced on antifungal microbial therapy. Two days later, she developed again left side pneumothorax, which was again managed by left intercostal drain. We were unable to wean her off from mechanical ventilatory support due to a significant air leak due to bronchopleural fistula. A posterolateral thoracotomy was performed, and the bronchopleural fistula was closed. She was extubated the next day, and intercostal drains were removed on the 4th post-operative day.

1. Introduction

CARMIL 2 is a multi-domain cytosolic protein essential for cytoskeletal organization cell migration and has a significant role in T-cell signaling. Mutation in CARMIL 2 can lead to immunodeficiency disorder with variable phenotype presentations [1]. This primary immune deficiency in several patients has been reported with pathogenic variants in the capping protein regulator and myosin 1 linker 2 (CARMIL2), also described as RGD leucine-rich repeat tropomodulin and proline-rich -containing protein [2]. These patients can present with different clinical manifestations like recurrent respiratory infections, dermatitis, eczema, psoriasis, esophagitis, diarrhea. Such patients often require multiple hospitalizations due to recurrent infections [3,4]. This case has been reported in line with SCARE criteria [5].

2. Case report

A five -year-old girl was admitted with a three-week history of cough and shortness of breath. she has a past history of mild eczema and allergic rhinitis, and recurrent respiratory tract infection. Her chest X-ray showed left-side pneumothorax. CT scan of thorax revealed a left lung Pneumothorax and pleural collection Fig. 1 (A&B). Basic blood investigation showed decreased lymphocyte count. An immunologic evaluation was proceeded due to recurrent respiratory tract infection and persistent low lymphocyte count. Her immunoglobulins levels IgG, IgA were low, and IgM was normal. The lymphocyte subset result showed a decrease in all lines of lymphocytes; the oxidative essay was normal. Gene study (primary immune deficiency panel) revealed a positive for a mutation in the CARMIL 2 gene (c.2536_2548del p. leu846 serf*36. The multidisciplinary team decided to proceed with surgery due to persistent mechanical support and significant air leak. The pediatric surgeon performed VATS stapling of lung bullae and drainage of empyema. Patient clinical condition improved chest X-ray showed lung expansion. Pleural fluid culture for positive for candida Albicans and staphylococcus epidermis, sensitive to Fluconazole and vancomycin, respectively. While the blood culture was positive for Gram-Positive cocci, and PCR was positive for cytomegalovirus. She was commenced on triple therapy antifungal (Fluconazole 240 mg intravenous (I/V) once daily), antimicrobial (Vancomycin 200mg I/V six hourly for seven days, Clindamycin 199 mg I/V six-hourly Antiviral Ganciclovir 100 mg I/V

* Corresponding author.
E-mail address: ikram.chaudhry@kfsh.med.sa (I.H. Chaudhry).

https://doi.org/10.1016/j.amsu.2021.102443
Received 29 April 2021; Received in revised form 19 May 2021; Accepted 23 May 2021
Available online 6 June 2021
2049-0801/© 2021 Published by Elsevier Ltd on behalf of IJS Publishing Group Ltd. This is an open access article under the CC BY license
twelve hourly. She also received intravenous immunoglobulin IgG 5% 20 gm stat followed by monthly dose. Two days later, she again developed left pneumothorax, chest drain was inserted. We were unable to wean off mechanical ventilatory support due to a significant prolonged air leak Fig. 1(C&D). A thoracic surgeon was consulted, and he proceeded for surgical closure of bronchopleural fistula through left posterolateral thoracotomy. The fistula was closed with interrupted 3/0 dexon sutures and reinforced with pedicled intercostal muscle flap. The wound was closed in layers, and one chest drain was left in the pleural cavity. Post-operatively there was no further air leak, and we were able to wean her off from the ventilator. The chest drain was removed after four days, and the patient was discharged home after one week for further follow-up in outpatient. Her follow-up chest x-ray and CT scan of the thorax were normal Fig. 1(E and F) She is followed up by internal medicine and immunologist for further care. She continue to receive 5% Immunoglobulin 20 gm on monthly bases.

3. Discussion
CARMIL2 deficiency is a genetic disease reported as part of primary immune deficiency in which there is pathogenetic variation in capping protein regulator and myosin one linker two, also called RGD. This is an autosomal recessive disease more prevalent in countries (Tunisia, Morocco, Turkey, Norway, Brazil, Saudi Arabia) where inter-family marriages are common. Patients with CARMIL2 mutation can present with heterogeneous clinical manifestations. Anas et al. reported seven cases of CARMIL2 in Saudi families with clinical manifestation as eczema, dry and scaly dermatitis and recurrent skin abscesses, recurrent respiratory infections, and bronchiectasis [6] Sorte et al. identified four cases of CARMIL2 genetic disease in Norwegian families they presented with phenotype skin warts, dermatitis, and molluscum contagious [7]. Schober et al. also described four cases of CARMIL2 gene mutation presented with Epstein-Barr-virus-related disseminated smooth muscles tumor [8].

Wong et al. described six cases of CARMIL2 mutation in different families [9]. To date, 24 cases have been reported in medical literature.
prolonged mechanical ventilatory support due to bronchopleural fistula, deficiency CARMIL2 disease in 6 years old girl who had a pneumothorax and discharged home on the fourth post-operative day for further challenging; we successfully repaired the Bronchopleural fistula using a and recurrent bacterial and fungal respiratory infection. She required have been reported to date (Table 1). We report a rare case of immune deficiency. All these genetic disease lead to defect in actin formation and -Table 1 . Mutation in CARMIL2 is also described in association with combined immune deficiency syndrome [10,11]. The patients with disease usually present with recurrent dermatitis, eczema, and dermal abscesses; other clinical manifestations include upper and lower respiratory tract infection, eosinophilic esophagitis, chronic diarrhea (colitis), EBV viremia, food allergy, asthma, and allergic rhinitis, and failure to thrive [12]. The best diagnostic laboratory tool is gene study and Immunophenotyping, which shows a decrease in overall patient regulatory T Cell and low or absent T-cell proliferation upon CD3/CD28 stimulation, skewing towards naïve form [13-15]Early diagnosis is essential to start immunoglobulin and appropriate antimicrobial therapy. The differential diagnosis in such cases is combined immune deficiency syndromes such as CARMIL2, Wiskott-Aldrich and DOCK8 deficiency. All these genetic disease lead to defect in actin formation and are required of TCR signaling (T Cell Receptor) [16]. Recurrent respiratory infection can lead to pleural effusion, pneumonia, pneumothorax, and empyema. Bronchopleural fistula (BPF) has never been reported in patients with CARMIL2 disease. Surgical closure of BPF is challenging in such cases due to immune deficiency, fragile tissues, and propensity towards bacterial and fungal infections. Baro trauma due to Mechanical ventilation is another added risk in such cases. In conclusion, in medical literature, 23 cases of CARMIL2 mutation have been reported to date (Table 1). We report a rare case of immune deficiency CARMIL2 disease in 6 years old girl who had a pneumothorax and recurrent bacterial and fungal respiratory infection. She required prolonged mechanical ventilatory support due to bronchopleural fistula, which has never been reported before. Surgery in such cases is very challenging; we successfully repaired the Bronchopleural fistula using a pedicle intercostal muscle flap. The patient was extubated the next day and discharged home on the fourth post-operative day for further follow-up in outpatient.

Table 1. Mutation in CARMIL2 is also described in association with combined immune deficiency syndrome [10,11]. The patients with disease usually present with recurrent dermatitis, eczema, and dermal abscesses; other clinical manifestations include upper and lower respiratory tract infection, eosinophilic esophagitis, chronic diarrhea (colitis), EBV viremia, food allergy, asthma, and allergic rhinitis, and failure to thrive [12]. The best diagnostic laboratory tool is gene study and Immunophenotyping, which shows a decrease in overall patient regulatory T Cell and low or absent T-cell proliferation upon CD3/CD28 stimulation, skewing towards naïve form [13-15] Early diagnosis is essential to start immunoglobulin and appropriate antimicrobial therapy. The differential diagnosis in such cases is combined immune deficiency syndromes such as CARMIL2, Wiskott-Aldrich and DOCK8 deficiency. All these genetic disease lead to defect in actin formation and are required of TCR signaling (T Cell Receptor) [16]. Recurrent respiratory infection can lead to pleural effusion, pneumonia, pneumothorax, and empyema. Bronchopleural fistula (BPF) has never been reported in patients with CARMIL2 disease. Surgical closure of BPF is challenging in such cases due to immune deficiency, fragile tissues, and propensity towards bacterial and fungal infections. Baro trauma due to Mechanical ventilation is another added risk in such cases.

In conclusion, in medical literature, 23 cases of CARMIL2 mutation have been reported to date (Table 1). We report a rare case of immune deficiency CARMIL2 disease in 6 years old girl who had a pneumothorax and recurrent bacterial and fungal respiratory infection. She required prolonged mechanical ventilatory support due to bronchopleural fistula, which has never been reported before. Surgery in such cases is very challenging; we successfully repaired the Bronchopleural fistula using a pedicle intercostal muscle flap. The patient was extubated the next day and discharged home on the fourth post-operative day for further follow-up in outpatient.

Ethical approval
IRB.

Source of funding
None.

Author contribution
Ikram ul Haq Chaudhry Thoracic surgeon, performed second operation drafting article.
Ahmed Alshaer wrote abstract.
Burair Al Jassas Wrote part of case report.

I.H. Chaudhry et al.  
Annals of Medicine and Surgery 66 (2021) 102443

Table 1  
Total number of cases of Novel CARMIL2 Mutation to date = 24.

| Author          | No of Cases | Clinical Manifestation                                      |
|-----------------|-------------|-------------------------------------------------------------|
| Sorte et al., 2016 | 4           | Dermatitis, warts, Molluscum contagiosum                     |
| Wong et al., 2016 | 6           | Cutaneous and pulmonary, allergy, TB, fungal infection       |
| Schober et al., 2017 | 4           | Epstein-Barr viremia, muscle tumors                          |
| Anas et al., 2018 | 7           | Eczema, dry dermatitis, skin abscesses                       |
| Alina et al., 2019 | 1           | Infantile colitis                                            |
| David K et al., 2019 | 1           | Smooth muscle tumors and eosinophilic esophagitis.           |
| Chaudhry et al., 2021 | 1           | Dermatitis, respiratory tract infection, and Eczema.         |
|                 |             | Allergic Rhinitis Respiratory tract infection, Bronchopleural fistula |

References
[1] David Kim, Asyegul Uner, Arzu Saglam, Amy Chadburn, Genevieve M. Crane, Peripheral Eosinophilia in primary immunodeficiencies of Actin dyeregulation: a case series of Wiskott-Aldrich syndrome. CARMIL2 and DOCK8 deficiency and review of the literature, Ann. Diagn. Pathol. 43 (2009), 1092-151413;1-7.
[2] M. R Ronzagli, N Jarmyszynski Cucchetti, C. Gregoire, E. Berget, A. Audebert, et al., The scaffolding function of PLTPR protein explains the essential role for CD28 costimulation in mouse and human T cells, J. Exp. Med. 213 (11) (2016) 2437-2457.
[3] R. Ronzagli, M. Cucchetti, N. Jarmyszynski, C. Gregoire, S. Berget Audebert, et al., The scaffolding function of PLTPR protein explains its essential role for CD 28 costimulation in mouse and human T Cells, J. Exp. Med. 213 (2016) 2437-2457.
[4] A. Chan, J. Basseti, E. Feuille, A case of recurrent aspiration pneumonia and persistent opisthia, in: Medically challenging causes/Ann Allergy Asthma Immunol 121, 2018, 563-4134.
[5] R.A. Agha, C. Franchi, C. Suhrahi, G. Mathew, For the SCARE GROUP, The scare 2020 Guidelines updating consensus surgical case report(scare) guidelines, Int. J. Surg. 84 (2020) 226–230.
[6] A.M. Alazami, Helaie Al, S. Alhiisi, B. Al Saud, H. Aljaian, D. Monies, S. Zeeshan, A.H. Mohamed, A. Rand, A. Hasan, S.A. Nouf, S. Farruh, A. Hamood, Novel CARMIL2 mutations in patients with variable clinical dermatitis, infections, and combined immunodeficiency, Front. Immunol. 9 (203) (2018) 1-11.
[7] H.S. Sorte, I.T. Owens, B. Fervane, P. Aukrest, H.C. Ercicshen, P.H. Bacek, et al., A potential founder variant in CARMIL2/PLTPR in three Norwegian families with warts, molluscum contagiosum, and T cell dysfunction, Mol. Genet. Genom. Med. 4 (2016) 604-616.
[8] T. Schober, T. Magg, M. Laschinger, M. Rolhfs, M.D. Linhares, J. Puchalka, et al., A human immune deficiency syndrome caused by a mutation in CARMIL2, Nat. Commun. 8 (2017). PMD 28112205.
[9] Y. Wong, C.S. Ma, Y. Ling, A. Bousfiha, Y. Camcioglu, S. Jacquot, et al., Dual T cell- and B cell-intrinsic deficiency in humans with biallelic PLTPR mutations, J. Exp. Med. 213 (2016) 2413-2435.
[10] C.M. Rolfman, R. Samech, F. Kavadas, A. Nahum, I. Dalal, et al., I am defining combined immunodeficiency, J. Allergy Clin. Immunol. 130 (2012) 177-183.
[11] W. Al Herz, H. Al Mousa, Combined immunodeficiency the middle east experience, J. Allergy Clin. Immunol. 131 (2013) 658–660.

[12] K. Felgentreff, R. Perez. Becker, C. Speckmann, K. Schwarz, L. Kalwek, G. Markelj, et al., Clinical and immunological manifestations of patients with a typical severe combined immune deficiency, Clin. Immunol. 141 (2011) 73–82.

[13] Y. Matsuzaka, K. Okamoto, T. Mabuchi, M. Lizuka, A. Ozawa, A. Oka, et al., Identification expression analysis and polymorphism of a novel RLTPR gene encoding RGD motif tropomodulin domain and proline/leucine-rich regions, Gene 343 (2004) 291–304.

[14] M.H. Lanfer, P. McConnell, J.A. Cooper, Cell migration and invadopodia formation require a membrane-binding domain of CARMIL2, J. Biol. Chem. 291 (2016) 1076–1091.

[15] Maira E. Maccani, Castren Speckmann, Maximilian Heeg, Antonia Reimer, Fedirica Casetti, Cristina Has, Stephan Ehi, Carla N. Castro, Profound immune deficiency with severe skin disease is explained by concomitant novel CARMIL2 and PLECI loss of function of mutation, Clin. Immunol. 208 (2019) 108228.

[16] K.W. Williams, J.D. Milner, A.F. Freeman, et al., Eosinophilia associated disorders of immune deficiency or immune dysregulation, Immunol. Allergy Clin. N. Am. 35 (3) (2015) 523–544.