Mesonephric adenocarcinoma of the cervix with focal endometrioid adenocarcinoma of the uterus: A case report and literature review

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Introduction

Mesonephric carcinomas are derived from remnants of the paired mesonephric ducts. These remnants may present in the lateral walls of the cervix (%22), vagina, uterine corpus and meso-ovarium.[1] Mesonephric adenocarcinoma is a rare form of female tract malignancy, and to our knowledge, there are 56 cases (including our case) of cervical mesonephric adenocarcinoma published thus far. Presenting symptoms of the disease may vary. Due to the rarity of this cancer, histopathological misclassifications may occur. Treatment and prognosis of mesonephric adenocarcinomas are also not well known to this present day. Standard guidelines for the surgical and medical approach to this disease have not been established yet. We present a rare case of cervical mesonephric adenocarcinoma with a focal endometrioid endometrial adenocarcinoma component.

Case presentation

A 49-year old, gravida five para 2, patient was admitted to an outer center with abnormal uterine bleeding and abdominal distension. She had no significant medical history nor any relative diagnosed with malignancy. An immobile cervical mass was discovered during her bimanual pelvic examination. MRI (Magnetic resonance imaging) scan that was performed later on had revealed 7x4 cm diameter mass lesion at the level of cervical internal osse extending to the distal part of the cervix and that distinctively expanded endometrial cavity with a suspicious finding of posterior parametrial invasion. Histopathological evaluations performed by deep cervical punch biopsy and loop electrical excision procedure (LEEP) were interpreted as carcinosarcoma and squamous metaplasia with microgladular hyperplasia, respectively. The patient was then referred to our clinic for further evaluation.

The pathology department of our institute re-evaluated specimens. Mesonephric adenocarcinoma was the pre-operative diagnosis after a detailed evaluation based on immunohistochemical and morphological characteristics. Though, the cervical involvement of high-grade endometrial carcinoma could not be excluded either. Patient's serum cancer antigen 125 (CA 125: 111 U/mL) and cancer antigen 19-9 (CA 19-9: 106 U/mL) levels were increased, and alpha-fetoprotein (AFP, 3,77 IU/mL) and carcinoembryonic antigen (CEA: 0,81 ng/mL) levels were measured within normal limits.

Radical hysterectomy with bilateral salphingooferectomy, omentectomy with pelvic-paraaortic lymphadenectomy was performed due to suspicious parametrial involvement on MRI scan.

On gross examination, an endocervical mass with a lower uterine segment elongation, which measured 7.5x5x4 centimeters, was observed. The cut surface of the infiltrative mass showed whitish to tanned with focal hemorrhagic areas. The tumors' distance to the uterine serosa was 1 millimeter, and the tumor was 4 millimeters apart from the vaginal surgical margin at the closest point.

The microscopic evaluation of the lesion with Hematoxylin and Eosin (H&E) stain revealed two different components (Fig. 1A). Predominantly angulated glands lined by columnar cells, focally tubular and solid epithelioid areas at cervix was noted. Nuclei were mostly uniform with coarse chromatin and grooves. At the lower uterine segment, the tumor had a second component which had different morphology with back to back glands lacking intervening stroma, which resembles endometrioid adenocarcinoma. This second tumor area had a lower mitotic index and showed less atypia. The tumor had both lymphatic and vascular invasion; however, it did not show perineural invasion.

Strong positive immunostaining with paired-box gene 8 (PAX-8) was seen in two components. GATA3 and thyroid transcription factor-1 (TTF-1) also had highly positive nuclear immunostaining at the cervical part of the tumor (Fig. 2); however, it had only focal and weak immunostaining at the uterine part of the tumor. Cervical part of the tumor had luminal CD10 staining, and this part was negative with estrogen receptors (ER). Uterine part of the tumor was positive with ER (Fig. 1B) and negative with CD10, and it showed MLH-1 and PMS-2 loss immunohistochemically. Immunohistochemically, ARID1A loss was seen. Polymerase chain reaction (PCR) analysis was performed for KRAS mutation status, and it revealed KRAS mutation.

Other parts of the uterus were unremarkable. There were no metastatic diseases at pelvic and paraaortic lymph nodes and omentum. The tumor was diagnosed as mesonephric adenocarcinoma with focal well-differentiated endometrioid adenocarcinoma component, with the microscopic and immunohistochemical findings. The pathological stage was pT1b2 N0 Mx L1 V1 R0, and the FIGO grade was IB3.

Postoperative recovery was uneventful. The patient was discharged on the 4^{th} day of postoperative follow-up. According to the multidisciplinary team's decision involving gynecologists, medical oncologists, pathologists and radiologists, it was proposed to deliver two courses of chemotherapy (paclitaxel and carboplatin) followed by external beam radiotherapy with concomitant cisplatin therapy and also brachytherapy due to the aggressive nature of mesonephric cancer.

Discussion

In the present study, we presented a concomitant cervical mesonephric adenocarcinoma and a focal endometrioid adenocarcinoma case. Mesonephric carcinoma is a rare female genital tract malignancy.[1]It is even much less frequent when endometrioid adenocarcinoma accompanies, and according to our detailed research in the relevant literature, there is only one other case that was published before.[2] Mesonephric carcinomas arise from mesonephric duct remnants or mesonephric hyperplasias; therefore, the tumor epicenter is mostly embedded within the cervical wall where mesonephric remnants reside.[3] Mesonephric adenocarcinomas consist of many different histological patterns that may vary for each tumor, and that different histological patterns may be present together in various microscopic fields of the same tumor as well. On microscopic evaluations, tubular features are the most commonly observed type of pattern. Ductal/glandular and sarcomatoid patterns are other frequently seen histopathological types. There are also different types such as; retiform, sex cord-like, papillary, hobnail, glomeruloid, solid and sieve-like patterns that are much more seldom.[2] [4]Mesonephric carcinomas have mild to moderately pleomorphic nuclei with a variable mitotic activity.[4] On immunohistochemical analysis, these tumors were mostly found positive for GATA3, PAX8, and CD10, whereas the vast majority of the presented cases in relevant literature were negative for estrogen receptors (ER) and progesterone receptors (PgR) and unrelated to high-risk Human papillomavirus (HPV).[5] [6]

Available literature investigating mesonephric cervical adenocarcinomas is based on only a few case reports. 55 cases were documented in current literature describing the clinical course of mesonephric carcinoma of the cervix (Table 1). The calculated mean age of these cases was 53.3-years, and the age of the entire population had a range between 24 and 74 years old. The vast majority of them were diagnosed at stage IB (n=35, 63.6%). Even though the majority were diagnosed at an early stage, nine recurrences had been reported among those diagnosed at stage IB (n=9/35, 25.7%). Moreover, four patients were diagnosed at stage IB, who had recurrences, were under 40-years of age.[2] [7] [8]Besides, five patients at stage IB were lost on early

follow-up, having an average overall-survival (OS) of 41 months.[2 7-10]Most of the recurrences were recorded as distant site metastasis (n=10/18, 58.8%).[2 8 11-15]

The tendency to early recurrences at an early stage despite previous radical resections shows these tumors' aggressive nature. Nomoto et al. reported a case of cervical mesonephric adenocarcinoma treated with surgery and diagnosed with FIGO stage IB. A year later, the patient developed multiple lung metastases.[15] Likewise, Clement et al. reported a case of stage IB cervical adenocarcinoma treated with surgery that relapsed in the abdomen 12 months after the initial treatment.[2]

Lymph node positivity is an adverse prognostic factor in this tumor's clinical course, leading to shorter recurrence-free (RFS) and overall-survival (OS) rates recorded in current literature. Such that; within all patients who were treated by lymphadenectomy also, three of five patients (60%) having positive lymph nodes had recurrences much earlier compared to nine patients with recurrences within the negative-lymph node group (9/25; 36%) (lymph-node (+) average RFS: 8.3 (months) vs. lymph-node (-) average RFS: 26.3 (months)). Two patients having positive lymph-nodes deceased during the fifth and ninth months of postoperative follow-up.[8 12] Whereas, only four patients in the negative lymph-node group were lost as one of them also had been diagnosed with synchronous ovarian clear-cell carcinoma at an advanced stage.[2 9-11]

Detailed analysis of the current literature had demonstrated 23 different cases who were given adjuvant therapy and another 22 cases without any postoperative oncotherapy. According to the available data presented in those reviewed cases, nine patients who had been treated with adjuvant therapy had recurrences during the follow-up (n=9/23, 39.1%). Whereas in the non-adjuvant group, only six patients had been diagnosed with recurrences (n=6/22, 27.2%). Although there seems to be no statistically significant difference among these two groups in terms of recurrence rate (p=0,398; these two groups compared with chi-squared ($\chi 2$) test), it should be kept in mind that present knowledge considering postoperative short and long-term follow-up outcomes of these cases are lacking in order to reach a definite conclusion.

The majority of presented cases in the given literature were diagnosed at postoperative histopathological evaluations of resected specimens. This may be linked to subclinical presentation of the disease that the patient may present without any overt or suspicious findings during admission other than some non-specific physical complaints like abnormal uterine bleeding, pelvic distention, etc. The tumor may harbor non-pathognomonic radiological features that may be seen in other types of tumors as well. In this aspect, pre-operative tissue biopsy has the utmost importance in making a differential diagnosis. Mesonephric carcinoma of the cervix should be considered when encountering an unusual histological non-HPV related cervical carcinoma.

We performed lymph-node dissection for our case even though pre-operative radiological evaluations were found negative for lymph-node involvement. Regardless of the tumoral stage, we recommend lymph-node dissections and radical surgery for this type of tumor, considering its aggressive clinical course. We think that lymph-node dissection with total radical hysterectomy is essential for local control of the disease in order to achieve desirable postoperative outcomes.

Although current knowledge about the clinical pattern of mesonephric adenocarcinomas is scarce and thus further evaluations are needed to establish a standard attitude towards its management; we advocate the use of adjuvant therapy considering the highly aggressive nature of the disease, particularly considering some of the published cases that were diagnosed at an early stage with distant organ metastasis despite previously performed radical resections. Future studies involving higher patient populations will increase the experience of clinicians dealing with these tumors and will help to agree on a common consensus in management strategy.

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References

1. Ferry J, Scully R. Mesonephric Remnants, Hyperplasia, and Neoplasia in the Uterine Cervix. *Am J Surg Pathol* 1990;14(12):1100-1111.
2. Clement P, Young R, Keh P, Östör A, Scully R. A Report of Eight Cases, Including Four with a Malignant Spindle Cell Component.*Am J Surg Pathol* 1995;19(10):1158-1171.
3. Mirkovic J, Sholl L, Garcia E, Lindeman N, MacConaill L, Hirsch M et al. Targeted genomic profiling reveals recurrent KRAS mutations and gain of chromosome 1q in mesonephric carcinomas of the female genital tract. *Mod Pathol* 2015;28(11):1504-1514.
4. Montalvo N, Redrobán L, Galarza D. Mesonephric adenocarcinoma of the cervix: a case report with a three-year follow-up, lung metastases, and next-generation sequencing analysis. *Diagn Pathol*2019;14(1).
5. Pors J, Cheng A, Leo J, Kinloch M, Gilks B, Hoang L. A Comparison of GATA3, TTF1, CD10, and Calretinin in Identifying Mesonephric and Mesonephric-like Carcinomas of the Gynecologic Tract. *Am J Surg Pathol* 2018;42(12):1596-1606.
6. Stewart C, Crum C, McCluggage W, Park K, Rutgers J, Oliva E et al. Guidelines to Aid in the Distinction of Endometrial and Endocervical Carcinomas, and the Distinction of Independent Primary Carcinomas of the Endometrium and Adnexa From Metastatic Spread Between These and Other Sites. *Int J Gynecol Pathol* 2019;38:S75-S92.
7. McGee C, Cromer D, Greene R. Mesonephric carcinoma of the cervix — differentiation from endocervical adenocarcinoma. *Am J Obstet Gynecol* 1962;84(3):358-366.
8. Silver S, Devouassoux-Shisheboran M, Mezzetti T, Tavassoli F. Mesonephric Adenocarcinomas of the Uterine Cervix. *Am J Surg Pathol* 2001;25(3):379-387.
9. Valente P, Susin M. Cervical adenocarcinoma arising in florid mesonephric hyperplasia: Report of a case with immunocytochemical studies. *Gynecol Oncol* 1987;27(1):58-68.
10. Cavalcanti M, Schultheis A, Ho C, Wang L, DeLair D, Weigelt B et al. Mixed Mesonephric Adenocarcinoma and High-grade Neuroendocrine Carcinoma of the Uterine Cervix. *Int J Gynecol Pathol*2017;36(1):76-89.
11. Bagué S, Rodríguez I, Prat J. Malignant Mesonephric Tumors of the Female Genital Tract. *Am J Surg Pathol* 2004;28(5):601-607.
12. Ribeiro B, Silva R, Dias R, Patrício V. Carcinosarcoma of the uterine cervix: a rare pathological finding originating from mesonephric remnants. *BMJ Case Reports* . 2019;12(3):e227050.
13. Jiang L, Tong D, Feng Z, Liu K. Mesonephric adenocarcinoma of the uterine cervix with rare lung metastases: A case report and review of the literature. *World Journal of Clinical Cases*2020;8(9):1735-1744.
14. Montalvo N, Redrobán L, Galarza D. Mesonephric adenocarcinoma of the cervix: a case report with a three-year follow-up, lung metastases, and next-generation sequencing analysis. *Diagn Pathol*2019;14(1).
15. Nomoto K, Hayashi S, Tsuneyama K, Hori T, Ishizawa S. Cytopathology of cervical mesonephric adenocarcinoma: a report of two cases.*Cytopathology* 2012;24(2):129-131.
16. Buntine D. Adenocarcinoma of the uterine cervix of probable wolffian origin. *Pathology* 1979;11(4):713-718.
17. Stewart C, Taggart C, Brett F, Mutch A. Mesonephric Adenocarcinoma of the Uterine Cervix with Focal Endocrine Cell Differentiation.*Int J Gynecol Pathol* 1993;12(3):264-269.
18. Lang G, Dallenbach-Hellweg G. The Histogenetic Origin of Cervical Mesonephric Hyperplasia and Mesonephric Adenocarcinoma of the Uterine Cervix Studied with Immunohistochemical Methods. *Int J Gynecol Pathol* 1990;9(2):145-157.
19. Anagnostopoulos A, Ruthven S, Kingston R. Mesonephric adenocarcinoma of the uterine cervix and

literature review. *Case Reports*2012;2012(dec09 1):bcr0120125632-bcr0120125632.
20. Dierickx A, Göker M, Braems G, Tummers P, Van den Broecke R. Mesonephric adenocarcinoma of the cervix: Case report and literature review. *Gynecol Oncol Rep* 2016;17:7-11.
21. Fukunaga M, Takahashi H, Yasuda M. Mesonephric adenocarcinoma of the uterine cervix: A case report with immunohistochemical and ultrastructural studies. *Pathol Res Pract* 2008;204(9):671-676.
22. Kır G, Seneldir H, Kıran G. A case of mesonephric adenocarcinoma of the uterine cervix mimicking an endometrial clear cell carcinoma in the curettage specimen. *J Obstet Gynaecol* 2016;36(6):827-829.
23. Angeles RM, August CZ, Weisenberg E. Pathologic quiz case: an incidentally detected mass of the uterine cervix. Mesonephric adenocarcinoma of the cervix. *Arch Pathol Lab Med*2004;128(10):1179-1180.
24. Yap O, Hendrickson M, Teng N, Kapp D. Mesonephric adenocarcinoma of the cervix: A case report and review of the literature. *Gynecol Oncol* 2006;103(3):1155-1158.
25. Abdul-Ghafar J, Chong Y, Han HD, Cha DS, Eom M. Mesonephric Adenocarcinoma of the Uterine Cervix Associated with Florid Mesonephric Hyperplasia: A Case Report. *J Lifestyle Med* . 2013;3(2):117-120.
26. Menon S, Kathuria K, Deodhar K, Kerkar R. Mesonephric adenocarcinoma (endometrioid type) of endocervix with diffuse mesonephric hyperplasia involving cervical wall and myometrium: An unusual case report.*Indian J Pathol Microbiol* 2013;56(1):51.
27. Meguro S, Yasuda M, Shimizu M, Kurosaki A, Fujiwara K. Mesonephric adenocarcinoma with a sarcomatous component, a notable subtype of cervical carcinosarcoma: a case report and review of the literature.*Diagn Pathol* 2013;8(1).
28. Tseng CE, Chen CH, Chen SJ, Chi CL.Tumor rupture as an initial manifestation of malignant mesonephric mixed tumor: a case report and review of the literature. *Int J Clin Exp Pathol*2014;7(3):1212-1217.
29. Roma AA. Mesonephric carcinosarcoma involving uterine cervix and vagina: report of 2 cases with immunohistochemical positivity For PAX2, PAX8, and GATA-3. *Int J Gynecol Pathol*2014;33(6):624-629.
30. Tekin L, Yazici A, Akbaba E, Akin MN. Mesonephric adenocarcinoma of the uterine cervix: A case report and review of the literature. *J Pak Med Assoc* 2015;65(9):1016-1017.
31. Ditto A, Martinelli F, Bogani G, Gasparri M, Di Donato V, Paolini B et al. Bulky mesonephric adenocarcinoma of the uterine cervix treated with neoadjuvant chemotherapy and radical surgery: report of the first case. *Tumori* 2016;102(Suppl. 2):10.5301/tj.5000386.
32. Yeo MK, Choi SY, Kim M, Kim KH, Suh KS. Malignant mesonephric tumor of the cervix with an initial manifestation as pulmonary metastasis: case report and review of the literature. *Eur J Gynaecol Oncol*2016;37(2):270-277.
33. Papoutsis D, Sahu B, Kelly J, Antonakou A. Perivascular epithelioid cell tumor and mesonephric adenocarcinoma of the uterine cervix: an unknown co-existence. *Oxf Med Case Reports*2019;2019(1):omy115.
34. Kilic C, Comert GK, Yesil B, *et al* . Mesonephric adenocarcinoma of the uterine cervix: A case report. *The Turkish Journal of Gynecologic Oncology* 2016;(3):125-128.
35. Yi SW. Malignant mixed mesonephric tumor arising in mesonephric carcinoma: a case report with complete remission after concurrent chemoradiation therapy. *European Journal of Gynaecological Oncology* 2020;41(2):320.

Figure Legends

Figure 1: H&E (A) and ER (B): Transitional zone between mesonephric and endometrioid components. Mesonephric carcinoma component was seen on the left upper side with angulated glandular features and negative ER staining. Endometrioid carcinoma component was seen on the right lower side with confluent glands and positive ER staining. (H&E magnification x40, ER magnification x40) **Figure 2:** GATA3 : Mesonephric carcinoma component showed focal nuclear positivity with GATA3 (GATA3 magnification x200)

None declared. Completed disclosure of interest forms are available to view online as supporting information.

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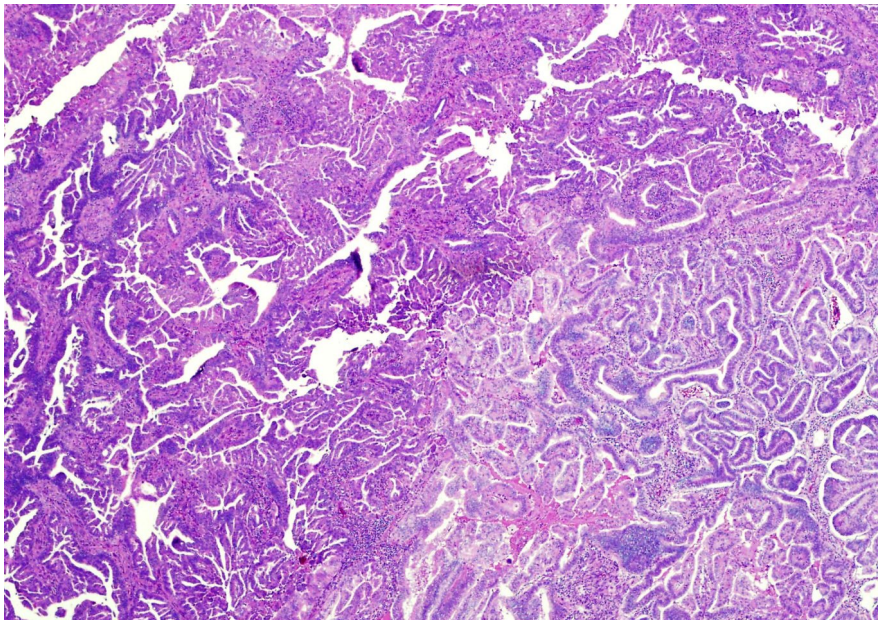

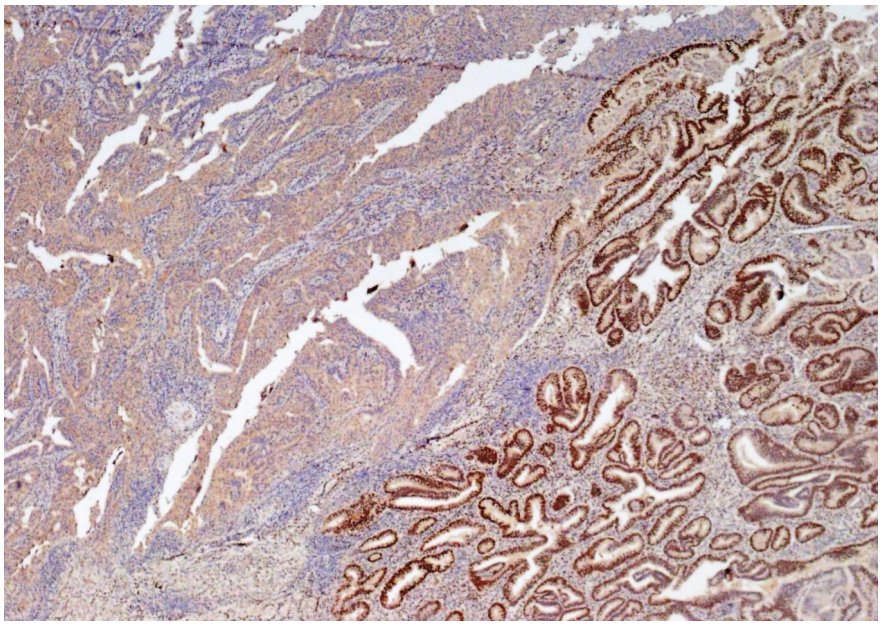

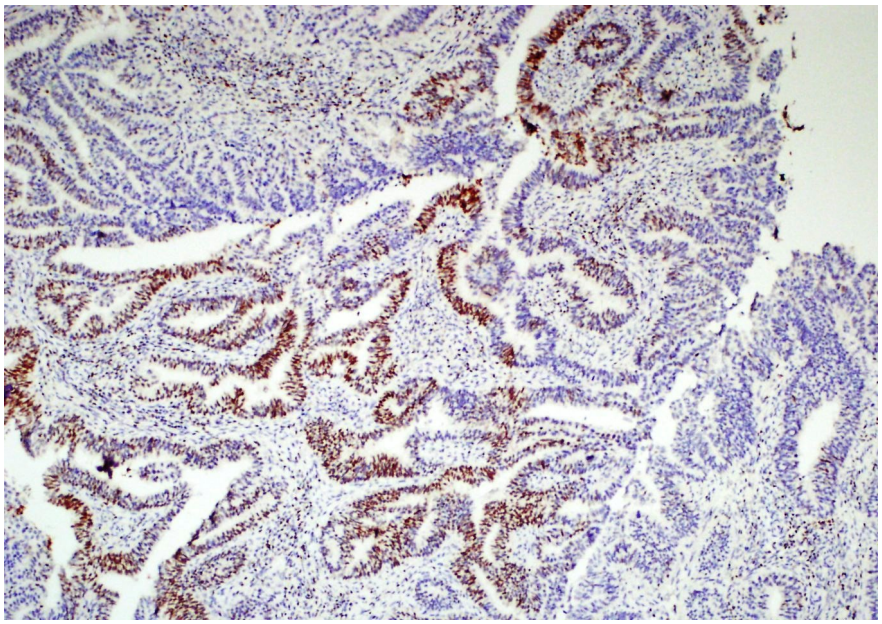

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Table 1 Summary of the cervical mesonephric adenocarcinoma cases1 2 4 7.docx available at https://authorea.com/users/471310/articles/562852-mesonephric-adenocarcinoma-of-the-cervix-with-focal-endometrioid-adenocarcinoma-of-the-uterus-a-case-report-and-literature-review