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Unique Presentations and the Psychosocial Aspects of the Management of an Unusual Case of Chimerism in Nepal: A Case Report

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Author's contribution

The sole author designed, analyzed, interpreted and prepared the manuscript.

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Case Report

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ABSTRACT

46XX/46XY is an exceptionally rare chimeric genetic condition characterized by the presence of some cells that express a 46XX karyotype and some cells that express a 46XY karyotype in a single human being. The incidence is not exactly known as the majority of diagnoses go unreported in the literature. Patients that express 46XX/ 46XY karyotype show a wide spectrum of different physical presentations, ranging from features of both male and female to a completely normal male or female phenotype. Hence, we present a case of a female hermaphrodite (75% 46 XX/ 25% 46 XY) karyotype who was raised as a phenotypic male. He possessed a uterus and an ovary on one side as internal genitalia and a micropenis, fused labia majoral fold as external genitalia. He presented to the Emergency with an acute abdomen which was subsequently diagnosed as hematometra and haematosalpinx and treated with total abdominal hysterectomy and right salphingo-oophorectomy. This case shows the importance of genetic analysis in the appropriate diagnosis of chimera, as well as the challenge of the sociocultural approach of them.

Keywords: Hermaphrodite; chimera; haematosalpinx; hematometra; 46 XX/46XY.

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1. INTRODUCTION

A genetic chimerism or chimera is a single organism composed of cells with more than one distinct genotype. A hermaphrodite is a person or animal having both male and female sex organs or other sexual characteristics. 46XX/46XY is an exceptionally rare chimeric genetic condition that can lead to hermaphroditism. It is characterized by the presence of some cells that express a 46 XX karyotype and some cells that express a 46 XY karyotype in a single human being [1]. The first human hermaphrodite chimera was reported in 1962 was a true hermaphrodite with one ovary and one ovotestis, and two different colored eyes, one brown and one hazel [2].

Relatively few chimeras have been reported since the first discovery. Yet there is a growing realization that chimerism may be more common than hitherto thought because most cases have been discovered accidentally [3,4]. The actual incidence of chimerism is unknown as most chimeras remain undetected. If both zygotes in a chimera are of the same sex, the individual will have a normal phenotype. [4,5]

As of date, there has not been a single case of chimerism reported in Nepal. This is the first case of chimera described in Nepal with a complete karyotyping confirmation and psychosocial counseling. Here is a case of female hermaphrodite (75% 46 XX/ 25% 46 XY) karyotype raised as a phenotypic male who came to attention due to an acute abdomen. He possessed a uterus and ovary on one side as internal genitalia, and a micropenis, fused labio-majoral fold as external genitalia. This case report aims to discuss the aspects of management and the challenges of social counseling while approaching chimera cases.

2. CASE REPORT

A twenty-six years old, unmarried, Hindu, illiterate driver from Dhanusa, Nepal raised as a male came to TUTH Emergency with complaints of pain in the right lower abdomen for 7 years (increased since the last 4 months) on April 3, 2017. On examination, he was found to have a well-developed breast (Tanner stage 4) (Fig 1), a cystic mass of 8 x 8 cm in the right iliac fossa, pubic hair, fused labio-majoral fold, non-canalized vagina, and a micropenis (Fig 2). USG/ MRI showed internal genitalia consisting of the right ovary had a biloculated cyst 8.1 x 7 x 4.8 cm along with uterus distended with fluid and debris (hematometra) (Fig 3 and Fig 4).

The patient reported that he had never had sexual intercourse in the past. He identified himself as a heterosexual male (he got erections and felt attracted to females). The patient had never menstruated. However, for the past seven years, he gave a history of dull lower abdominal pain with cyclic exacerbations. He didn't give any history of endocrine problems as well. There was no history of intake of any exogenous hormones.

Total abdominal hysterectomy with right salphingo-oophorectomy was done for a unicornuate uterus with hematometra and hematosalpinx on the personal preference to continue living as a man. Operative findings showed that the uterus was enlarged to 8 weeks size and a 10 cm retort-shaped mass arose from the right tube which lay twisted on itself. (Fig 5, Fig 6) The right ovary was visualized. The left tube and ovary were not present. On the cut section, the uterus released 15 ml of chocolate-colored fluid and the mass (haematosalpinx) also released 50 ml of chocolate-colored fluid (Fig 7).

Karyotype report came out as 46 XX (75%) and 46 XY (25%), establishing that this patient had an extremely rare chimeric genetic condition. The karyotype report was sent to SRL Diagnostic Laboratory in Nepal, however, the lab sent the sample to the corresponding laboratory in India for confirmation. The report came almost two months after the patient was already discharged. It is kept in the patient's medical records. Official report copy cannot be published respecting the policy of the clinic. The patient was called back to discuss the reports. Detailed family history was taken and there seemed to be no history of genetic abnormalities in the family. The patient and the family were counseled accordingly about the karyotype findings. The patient was again reviewed after six months. He was doing well and he continued living as a male. In the follow-up consultations, he didn't have any complaints and there seemed to be no long-term operative complications.

3. DISCUSSION

There are a few famous reports of chimerism detected accidentally that have caught a lot of scientific and media attention. The first was a case of a woman, Karen, who was told, following DNA tests of family members for a kidney donor, that two of her three sons could not be hers [6].

Another woman, Lydia, who claimed welfare for her children in Washington State, was accused

of fraud as DNA tests showed they were not her children. She was unable to obtain legal help as DNA evidence was considered irrefutable until her attorney came across the story of Karen. The story of the two women appeared on the Discovery Channel in May 2005 [7].

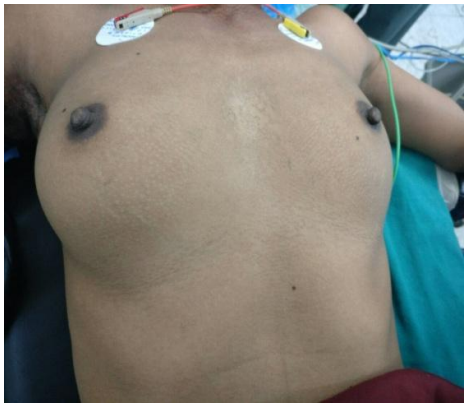

Fig. 1. Patient phenotype with Tanner stage 4 of breast development

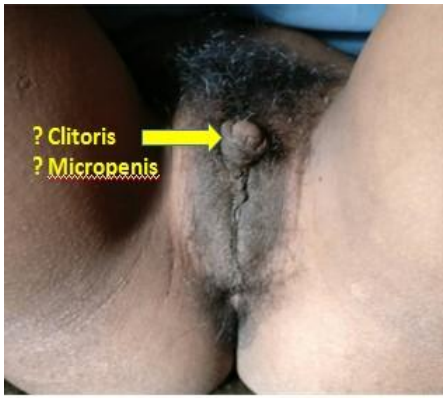

Fig. 2. Patient external genitalia Perineal inspection

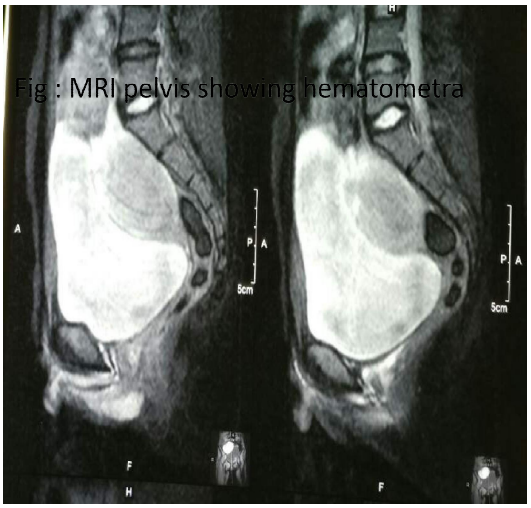

Fig. 3. MRI sagital T2 pelviareaea

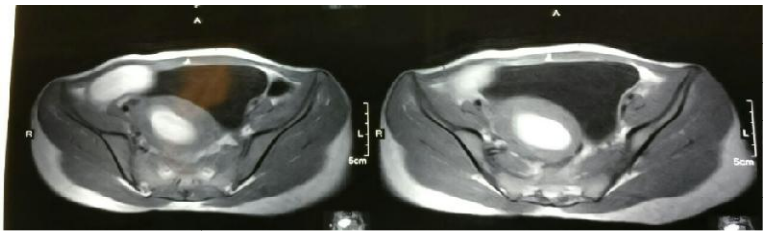

Fig. 4. MRI showing hematosaphinx

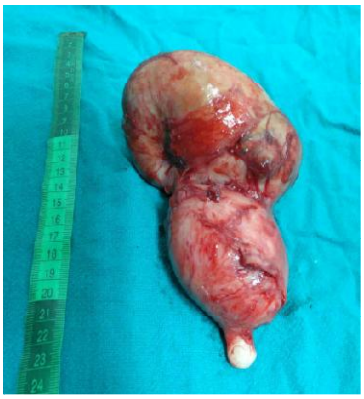

Fig. 5. Pathologic espécimen Uterus enlarged to 6 weeks size, 10x8cm retort shaped mass from the right tube which was twisted on itself, Right ovary not visualized, Left tube and ovary not present

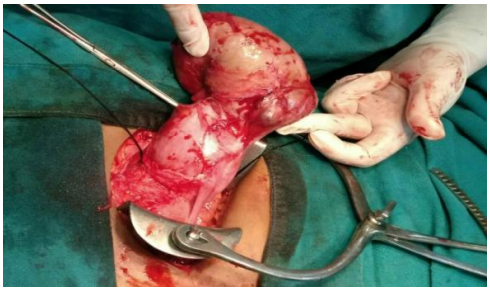

Fig. 6. Pathologic spécimen Uterus enlarged to 6 weeks size, 10x8cm retort shaped mass from the right tube which was twisted on itself, Right ovary not visualized, Left tube and ovary not present

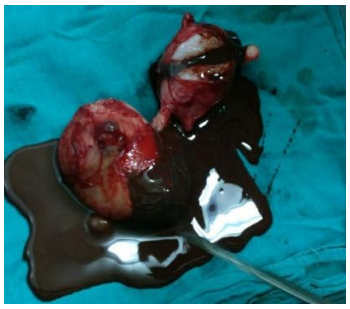

Fig. 7. Pathologic espécimen on Cut Section: Uterus released 15ml of chocolate-colored fluid, Mass released 50ml of chocolate-colored fluid(Hemathometra)

However, chimerism in which there is discordancy of sex is more easily detectable. Patients that express 46XX/ 46XY karyotype show a wide spectrum of different physical presentations, ranging from features of both male and female to a completely normal male or female phenotype [8]. The proportion of XY cells in the undifferentiated gonad is important as the Y chromosome can influence the behavior of a majority of neighboring cells that lack a Y chromosome. Individuals with XX as well as XY cells can therefore develop into hermaphrodites with different proportions of ovarian and testicular tissues [5].

As far as external genitalia is concerned, some may have a small phallus midway in size between a clitoris and a penis, or an incompletely closed urogenital opening (shallow vagina)' or an abnormal urethra opening on the perineum [9].

There is a dearth of literature on this topic, possibly because of the rarity of such a condition. There are three basic ways by which a fusion chimera can be formed:

1. The aggregation of two distinct blastocysts (one of which expresses 46XX and the other of which expresses 46 XY) into a single embryo, which subsequently leads to the development of a single individual with two distinct cell lines [1].

2. Sometimes a second polar body also gets fertilized by a sperm and zygote which results from this fusion then merges with a normally fertilized zygote. One of the zygotes has the XY karyotype and the other has XX [5].

3. Division of the female pronucleus and its subsequent fertilization and the formation of the two daughter cells by two spermatozoa. Then there is a fusion of the resulting zygotes. One of the zygotes has the XY karyotype and the other has XX (as sex is determined by the sperm) [5].

Chimeras with 46XX and 46 XY cell lines can have a normal male or a female phenotype depending on whether XY or the XX cells form the gonad. To date, only 28 out of 50 individuals with a 46 XX/ 46 XY karyotype were either true hermaphrodites or had ambiguous genitalia.[5].

Farag, et al., in 1987, presented a similar case of a thirteen-year-old female with ambiguous external genitalia, right inguinal ovotestis, left ovary, apparently normal Mullerian system, and absent Wolffian system. Cultured lymphocytes showed a 46XX/46XY karyotype. They concluded that the patient was a true hermaphrodite chimera [10].

Van Beyer Y, et al., in 2018, reported about an adult male initially presenting with gynecomastia and a painless scrotal mass without additional genital anomalies. He underwent gonadectomy because of suspected cancer. However, histological analyses revealed an ovotestis with ovulatory activity confirmed by immunohistochemistry with multiple markers. Karyotyping of cultured peripheral blood lymphocytes and a buccal smear revealed a 46XX/46XY chimeric constitution with different percentages [11].

In 2020, Kawamura also reported a case of a boy with ambiguous genitalia and hypospadias, showing 46 XY/46 XX in peripheral blood cells [12].

There have been no reported cases in which a patient with chimerism and hermaphroditism has presented with hematosalpinx and hematometra. In the index case, there seems to be concurrent genital tract obstruction which is unrelated to the chimeric status. This explains why the patient never had periods. It also explains the dull abdominal pain he had been having for the past seven years with cyclic exacerbations.

In patients that have a chimeric hermaphrodite status, psychosocial aspects should also be explored. The presence of ambiguous genitalia, ovotestes, chimerism, or mosaicism (of the sex chromosomes) may evoke confusion and discussion about one's gender in patients and parents. Gender mix-up is extremely stressful as patients and parents experience a loss of identity [11,13]. The sex assignment and treatment of such patients depend on the age at diagnosis, genital development, and the internal structures present [14].

There were many difficulties faced when dealing with this patient. The patient was female hermaphrodite, with late development of hematometra and hematosalpinx explained by one-sided development of the Mullerian tube with concurrent outflow tract obstruction. When the news of chimerism was broken to the patient, he responded in a more composed manner than expected. He said he knew something was not right because of his breasts, which he used to hide with tight clothes. He was glad that the

"female" organs were now removed. He was told about breast reduction surgery but he did not show interest as it seemed too expensive.

The literature describes a variety of presentations of phenotypes and gender identity on chimera cases [4,5]. Few cases decide to continue with the gender assigned at birth, while others identify themselves with the opposite gender after the diagnosis, and decide to change it [15]. In the index case, HE could have lived as a SHE because of well-developed breasts and possible reconstructive genital surgery. However, in this case, the decision to live as a male was sought more socially acceptable as the patient was brought up as a male and identified himself with the male gender. Sexual and gender determination and differentiation are complex; so above all the patient's preference should be regarded as most important—the karyotype alone must not be the sole basis [15].

In the present case, as the patient identified as a male, it was easier to counsel him and he was more satisfied with the treatment as the "female" organs were finally removed and he felt more like a "male". Sex discordant chimeras, on the other hand, are a bigger conflict in the psychosocial approach. An appropriate counseling and personalized treatment, open conversation with each patient are needed to get a complete picture and knowledge about the patient's feelings and expectations. The social taboos and judgment can also be a factor that influences some chimera patients to maintain the first gender. Hence, individual interviews are important, aside from family, to get the deep difference between real and social influence in gender identity [5].

4. CONCLUSION

A phenotypical male with gynecomastia and micropenis on physical examination presented with an acute episode of abdominal pain, which was identified as hematometra and hematosalphinx after radiography. Karyotype revealed a rare chimeric condition, which caused the hermaphroditism in this patient. The patient underwent surgery for the hematometra and hematosalphinx, which lead to the removal of his Mullerian internal genitalia. Post-treatment, the patient felt more like a "male".

Chimerism should be suspected in all patients presenting with hermaphroditism. If confirmed, gender evaluation with timely re-assignment followed by genital repair in early childhood complemented by psychosocial counseling need to be considered appropriately in disorders of sex development. The sex assignment and treatment of such patients depend on the age at diagnosis, genital development, and the internal structures present.

CONSENT

As per international standard or university standard, patients' written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

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COMPETING INTERESTS

Author has declared that no competing interests exist.

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