A report of nine cases and review of the literature of infertile men carrying balanced translocations involving chromosome 5

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Abstract

Background: Balanced translocations may cause the loss of genetic material at the breakpoints and may result in failure of spermatogenesis. However, carriers of reciprocal translocation may naturally conceive. Genetic counseling of male carriers of translocations remains challenging. This study explores the clinical features of carriers of chromosome 5 translocations, enabling informed genetic counseling of these patients.

Results: Of 82 translocation carriers, 9 (11%) were carriers of a chromosome 5 translocation. One case had azoospermia, while three cases had experienced recurrent spontaneous abortions, two cases had each experienced stillbirth, and three cases produced a phenotypically normal child confirmed by amniocentesis. A literature review identified 106 patients who carried chromosome 5 translocations. The most common chromosome 5 translocation was t(4,5), observed in 13 patients. Breakpoint at 5p15 was observed in 11 patients. All breakpoints at chromosome 5 were associated with gestational infertility.

Conclusion: In genetic counseling, physicians should consider chromosome 5 and its breakpoints. Carriers of chromosome 5 translocations may continue with natural conception or use assisted reproductive technologies, such as preimplantation genetic diagnosis.

Keywords: Male infertility, Chromosome 5, Balanced translocation, Breakpoint, Genetic counseling

Background

Known chromosomal alterations play a major role in perturbing male fertility [1]. Reciprocal chromosomal translocations are the most common structural rearrangement, with an incidence in infertile males up to ten times higher than in fertile men [2]. Balanced chromosomal translocations may cause the loss of genetic material at breakpoints and may result in failure of spermatogenesis [3]. Individuals affected by such translocations exhibit reproductive problems such as infertility, recurrent pregnancy loss, and malformed offspring [4, 5]. These effects are related to the specific chromosomes and breakpoints involved in the translocation [6, 7]. Some breakpoints can disrupt the structure of an important gene, leading to spermatogenic or maturation disorders, and male infertility [5]. Important genes associated with male infertility are located on chromosome 5. For example, Camk4 (encoding Ca^{2+}/calmodulin-dependent protein kinase IV) is located on chromosome 5q22.1, and is expressed in spermatids and associated with chromatin and nuclear matrix [8]. Disrupted CAMK4 expression may be associated with human male infertility [8]. In addition, the Spink13 gene (encoding serine protease inhibitor, Kazal-type 13), mapped on chromosome 5 at 5q32, was reported to be associated with sperm maturation [9]. The breakpoint of 5p13 was shown to be related to impaired spermatogenesis [10].

However, genetic counseling of male carriers of chromosomal translocations remains challenging. Preimplantation genetic diagnosis (PGD) is recommended for those exhibiting a balanced translocation. Microdissec tion testicular sperm extraction and in vitro fertilization accompanied by PGD increases the chance of these carriers fathering a healthy child [11, 12]. Clinical characteristics, including spontaneous abortion, do not differ between those couples who accept and those who decline PGD [13]. A systematic review showed there was
insufficient evidence that PGD improves the live birth rate in couples with repeated miscarriage and carrying a structural chromosome abnormality [14]. In addition, the live birth rate in patients refused PGD and choosing to conceive naturally was reported to be 37–63% for the first pregnancy, and then a cumulative rate of 65–83% [4]. Natural pregnancy success rates for couples in which the male carries a chromosomal translocation ranged from 30% to 70% [15]. This suggests that continued attempts to conceive naturally are a viable option for successful pregnancy, however, the relationship between clinical features and chromosome structural abnormality warrants further study.

The present study was established to explore the clinical features and translocation breakpoints in carriers of balanced translocations involving chromosome 5. This paper also highlights the importance of genetic counseling for infertile men.

**Methods**

**Patients**

Between July 2010 and December 2016, 82 male carriers of chromosomal translocations who were experiencing infertility, or receiving counseling, were recruited from the outpatient’s department at the Center for Reproductive Medicine, the First Hospital of Jilin University, Changchun, China. All patients underwent a thorough physical examination and semen analysis, and were required to complete a detailed questionnaire regarding their smoking habits, marital status, medical history, and working conditions. The study protocol was approved by the Ethics Committee of the First Hospital of Jilin University, and written informed consent was obtained from all participants.

**Semen analysis**

Semen analysis was performed according to procedures recommended by the World Health Organization guidelines. If no sperm was found, sperm was analyzed by sedimenting semen samples through centrifugation. Patients with oligozoospermia were diagnosed as a sperm count less than $15 \times 10^6$/ml in their last three semen samples (taken at intervals of 1–3 weeks). Azoospermia and oligozoospermia were defined as previously described [5]. All analyses were performed at the same laboratory, and all data were accessed from medical records.
| Case | Karyotype | Breakpoints | Clinical findings | Reference |
|------|-----------|-------------|------------------|-----------|
| 1    | t(1;5)    | 1p32;5q31   | Severe oligoasthenoteratozoospermia | Peschka et al., 1999 [27] |
| 2    | t(1;5)    | 1p31.1;5q33.3 | Normozoospermia | Brugnon et al., 2006 [28] |
| 3    | t(1;5)    | 1p22.5q11   | Malformed/stillborn children | Meza-Espinoza et al., 2008 [29] |
| 4    | t(1;5)    | 1q36.1;5q31 | 2 miscarriage, PGD and 2 term delivery | Ikuma et al., 2015 [4] |
| 5    | t(1;5)    | 1q41.5q33   | Miscarriage and PGD | Kyu Lim et al., 2004 [30] |
| 6    | t(1;5)    | 1qter;5p14  | Recurrent miscarriage | Goud et al., 2009 [31] |
| 7    | t(2;5)    | 2p25;5p12   | Teratozoospermia, Habitual abortions | Vegetti et al., 2000 [32] |
| 8    | t(2;5)    | 2p21.5p15   | Recurrent spontaneous abortion | Gada Saxena et al., 2012 [33] |
| 9    | t(2;5)    | 2p13.5p15   | Recurrent fetal wastage | Fryns et al., 1998 [34] |
| 10   | t(2;5)    | 2p11.5q15   | Abortion | Templado et al., 1988 [35] |
| 11   | t(2;5)    | 2p11.5q31   | Recurrent abortion | Poirnoi et al., 1988 [36] |
| 12   | t(2;5)    | 2q12.5q35.3 | Recurrent pregnancy loss | Kochhar et al., 2013 [22] |
| 13   | t(2;5)    | 2q13.1;5q35.1 | 6 miscarriage, PGD and 1 term delivery | Ikuma et al., 2015 [4] |
| 14   | t(3;5)    | 3p27.5p14   | 4 fetal losses | Adamoli et al., 1986 [37] |
| 15   | t(3;5)    | 3q13.5q35   | Repeated abortions | Venkateshwarli et al., 2011 [21] |
| 16   | t(3;5)    | 3q26.2p15.1 | Miscarriage | Sugiuara-Ogasawara et al., 2008 [38] |
| 17   | t(3;5)    | 3q27.5p15   | Normozoospermia, A boy 46,XY,t(3;5)pat | Vozdova et al., 2013 [11] |
| 18   | t(3;5)    | 3q28.5p13   | Recurrent spontaneous abortion | Gada Saxena et al., 2012 [33] |
| 19   | t(3;5)    | 3q29.5q13   | Multiple abortions | Castle et al., 1988 [39] |
| 20   | t(3;5)    | 3q29.5q33.2 | PGD | Findikli et al., 2003 [40] |
| 21   | t(4;5)    | 4p15.2;5p12 | Normozoospermia | Wiland et al., 2007 [41] |
| 22   | t(4;5)    | 4p15.5q12   | Oligozoospermia | Perrin et al., 2010 [42] |
| 23   | t(4;5)    | 4p14.5q13.1 | recurrent miscarriage | Pundir et al., 2016 [43] |
| 24   | t(4;5)    | 4q21.5p15   | Habitual miscarriage | Li et al., 2012 [23] |
| 25   | t(4;5)    | 4q21.5p15   | Recurrent spontaneous abortion | Zhang M et al., 2015 [44] |
| 26   | t(4;5)    | 4q21.5q11.2 | Severe oligoasthenoteratozoospermia | Peschka et al., 1999 [27] |
| 27   | t(4;5)    | 4q22.5q35   | 2 fetal losses | Adamoli et al., 1986 [37] |
| 28   | t(4;5)    | 4q25.5p15.2 | 4 abortions | Ghazaey et al., 2015 [45] |
| 29   | t(4;5)    | 4q31.5p15   | Recurrent spontaneous abortions | Zhang et al., 2011 [46] |
| 30   | t(4;5)    | 4q31.5q13   | normozoospermia | Huang et al., 2007 [47] |
| 31   | t(4;5)    | 4q32.5q14   | Oligoasthenoteratozoospermia | Dohle et al., 2002 [48] |
| 32   | t(4;5)    | 4q32.5q14   | Miscarriage | Dul et al., 2012 [49] |
| 33   | t(4;5)    | 4q35.5p15   | Recurrent miscarriages | Dutta et al., 2011 [50] |
| 34   | t(5;6)    | 5p15.3q6q13 | recurrent abortion | Kiss et al., 2009 [51] |
| 35   | t(5;6)    | 5p13.6q27   | Recurrent spontaneous abortion | Gada Saxena et al., 2012 [33] |
| 36   | t(5;6)    | 5q21.6q33   | Recurrent fetal wastage | Fryns et al., 1998 [34] |
| 37   | t(5;6)    | 5q33.1;6p11.2 | Miscarriage | Sugiuara-Ogasawara et al., 2008 [38] |
| 38   | t(5;6)    | 5q35.6p21.3 | PGD | Ko et al., 2010 [52] |
| 39   | t(5;7)    | 5p15.2;7p14 | Recurrent spontaneous abortion | Gada Saxena et al., 2012 [33] |
| 40   | t(5;7)    | 5p13.7p15   | Recurrent pregnancy loss | Kochhar et al., 2013 [22] |
| 41   | t(5;7)    | 5p13.7p15   | Spontaneous abortion | Stephenson et al., 2006 [53] |
| 42   | t(5;7)    | 5p11.7q11   | 8 abortions | Al-Hussain et al., 2000 [54] |
| 43   | t(5;7)    | 5q13.7p15.1 | 2 miscarriages | Estop et al., 1995 [55] |
| 44   | t(5;7)    | 5q21.7q32   | Normozoospermia | Cifuentes et al., 1999 [56] |
| Case | Karyotype | Breakpoints | Clinical findings | Reference |
|------|-----------|-------------|-------------------|-----------|
| 45   | t(5;7)    | 5q33;7q22   | Miscarriage and PGD | Kyu Lim et al., 2004 [30] |
| 46   | t(5;8)    | 5p14;8q22   | Asthenozoospermia  | Godo et al., 2013 [7] |
| 47   | t(5;8)    | 5q22;8q24.1 | Oligoasthenoteratozoospermia | Meschede et al., 1998 [57] |
| 48   | t(5;8)    | 5q22.1;8q23.2 | PGD | Ko et al., 2010 [52] |
| 49   | t(5;8)    | 5q23.1;8p23.2 | 4 miscarriage, 1 term delivery | Ikuma et al., 2015 [4] |
| 50   | t(5;8)    | 5q33.3;8q11.21 | Recurrent miscarriage | Pundir et al., 2016 [43] |
| 51   | t(5;8)    | 5q33;8q13   | Normozoospermia  | Blanco et al., 1998 [58] |
| 52   | t(5;8)    | 5q33;8q13   | Normozoospermia  | Estop et al., 2000 [59] |
| 53   | t(5;8)    | 5q33;8q13   | Normozoospermia  | Godo et al., 2013 [7] |
| 54   | t(5;8)    | 5q33;8q13   | Normozoospermia  | Anton et al., 2008 [60] |
| 55   | t(5;8)    | 5q33.1;8p11.2 | Asthenozoospermia | Anton et al., 2008 [60] |
| 56   | t(5;8)    | 5q33.3;8q22.1 | Recurrent fetal wastage | Fryns et al., 1998 [34] |
| 57   | t(5;8)    | 5q15.1;9q22.1 | Normospermic, Primary infertility | Vozdova et al., 2013 [11] |
| 58   | t(5;8)    | 5q10;9q10   | Recurrent spontaneous abortions | Rouen et al., 2017 [62] |
| 59   | t(5;8)    | 5q21;9q14   | 2 fetal losses | Adamoli et al., 1986 [37] |
| 60   | t(5;8)    | 5q22;10q11.2 | PGD | Ko et al., 2010 [52] |
| 61   | t(5;8)    | 5q22.1;10q22 | Spontaneous abortion | Stephenson et al., 2006 [53] |
| 62   | t(5;8)    | 5q34;10p12.1 | Normozoospermia | Zhang et al., 2014 [61] |
| 63   | t(5;9)    | 5p13;9q22   | PGD | Zhang et al., 2014 [61] |
| 64   | t(5;9)    | 5q10;9q10   | Recurrent spontaneous abortions | Rouen et al., 2017 [62] |
| 65   | t(5;9)    | 5q21;9q14   | 2 fetal losses | Adamoli et al., 1986 [37] |
| 66   | t(5;9)    | 5q23.2;9q22.3 | Spontaneous abortion | Stephenson et al., 2006 [53] |
| 67   | t(5;9)    | 5q33;9p24   | Recurrent miscarriage | Iyer et al., 2007 [63] |
| 68   | t(5;9)    | 5p13.3;10p12.2 | PGD | Ko et al., 2010 [52] |
| 69   | t(5;10)   | 5p13;9q22   | PGD | Zhang et al., 2014 [61] |
| 70   | t(5;10)   | 5q10;9q10   | Recurrent spontaneous abortions | Rouen et al., 2017 [62] |
| 71   | t(5;10)   | 5q21;9q14   | 2 fetal losses | Adamoli et al., 1986 [37] |
| 72   | t(5;10)   | 5q22.1;10q22 | Spontaneous abortion | Stephenson et al., 2006 [53] |
| 73   | t(5;10)   | 5q34;10p12.1 | Recurrent spontaneous abortions | Rouen et al., 2017 [62] |
| 74   | t(5;10)   | 5q34;10p12.1 | Recurrent spontaneous abortions | Rouen et al., 2017 [62] |
| 75   | t(5;10)   | 5q34;10p12.1 | Recurrent spontaneous abortions | Rouen et al., 2017 [62] |
| 76   | t(5;10)   | 5q34;10p12.1 | Recurrent spontaneous abortions | Rouen et al., 2017 [62] |
| 77   | t(5;10)   | 5q34;10p12.1 | Recurrent spontaneous abortions | Rouen et al., 2017 [62] |
| 78   | t(5;10)   | 5q34;10p12.1 | Recurrent spontaneous abortions | Rouen et al., 2017 [62] |
| 79   | t(5;10)   | 5q34;10p12.1 | Recurrent spontaneous abortions | Rouen et al., 2017 [62] |
| 80   | t(5;10)   | 5q34;10p12.1 | Recurrent spontaneous abortions | Rouen et al., 2017 [62] |
| 81   | t(5;10)   | 5q34;10p12.1 | Recurrent spontaneous abortions | Rouen et al., 2017 [62] |
| 82   | t(5;10)   | 5q34;10p12.1 | Recurrent spontaneous abortions | Rouen et al., 2017 [62] |
| 83   | t(5;10)   | 5q34;10p12.1 | Recurrent spontaneous abortions | Rouen et al., 2017 [62] |
| 84   | t(5;10)   | 5q34;10p12.1 | Recurrent spontaneous abortions | Rouen et al., 2017 [62] |
| 85   | t(5;10)   | 5q34;10p12.1 | Recurrent spontaneous abortions | Rouen et al., 2017 [62] |
| 86   | t(5;10)   | 5q34;10p12.1 | Recurrent spontaneous abortions | Rouen et al., 2017 [62] |
| 87   | t(5;10)   | 5q34;10p12.1 | Recurrent spontaneous abortions | Rouen et al., 2017 [62] |
| 88   | t(5;10)   | 5q34;10p12.1 | Recurrent spontaneous abortions | Rouen et al., 2017 [62] |
Cytogenetic analysis

Cytogenetic analysis was carried out on all patients. Peripheral blood (0.5 mL) was collected in sterile tubes containing 30 U/mL heparin. Lymphocytes were then cultured in appropriate culture medium (Yishengjun; Guangzhou Baidi Biotech, Guangzhou, China) for 72 h, and subsequently treated with 20 μg/mL colcemid for 1 h. G-banding of metaphase chromosomes and karyotype analysis were performed using previously described methods [5]. Twenty metaphases were counted and 6 karyotypes were analyzed per patient. Karyotype nomenclature was described in accordance of ISCN2009. The resolution level of chromosome analysis was 400–550 band levels.

Analysis of the identified translocation breakpoints

A search of translocations identified in chromosome 5 from infertile males was performed using PubMed. The keywords “chromosome / translocation / sperm” and “chromosome / translocation / abortion” were used for the PubMed search. The relationships of translocation breakpoints with male infertility and recurrent pregnancy loss were analyzed. Such searches were performed for a total of 106 carriers of chromosomal 5 translocations. This study included the cases of reciprocal chromosomal translocations involving chromosome 5 in reported papers, and excluded cases without breakpoints, females, newborns, and bone marrow detection involving chromosome 5.

Results

A total of 82 translocation carriers were detected in this study. Of these, nine (11%) were carriers of a chromosome 5 translocation, in which other chromosome abnormality had been excluded. Karyotype results and G-banding karyotypes from these nine patients are respectively summarized in Table 1 and Fig. 1. One case had azoospermia (pregestational infertility), while eight cases had normal semen. For the former, no AZF gene deletion was found. Of the latter eight cases, it was evident that their partners were able to conceive, but had a tendency to miscarry (gestational infertility): three cases had experienced recurrent spontaneous abortions, two cases each experienced stillbirths, and three cases produced a phenotypically normal child confirmed by amniocentesis. For the other 73 cases of translocations, we will describe or have published in another study.

A literature review was also performed, from which karyotype results, clinical manifestations, and breakpoints on chromosome 5 were collected, as shown in Table 2. A total of 106 karyotypes included chromosome 5 translocations. The most common translocation was t(4;5), observed in 13 patients, followed t(5;8) (N = 11). Chromosomes 4(N = 13), 8(N = 11), 2,3,7,13(N = 7), 1,9,10,12(N = 6), 6, 18(N = 5), 15,20(N = 4),14,16,17(N = 3) and 11,19, X (N = 1) were respectively involved in the balanced translocation with chromosome 5.

The most common breakpoint, at 5p15, was observed in 11 patients, followed by 5q13 (N = 10).
Breakpoints at 5p14, 5p11, 5q13, 5q14, 5q15, 5q22, 5q31, 5q35 and 5q35.1 were found with cases of both pregestational and gestational infertility. All breakpoints were associated with gestational infertility (Table 3).

**Discussion**

In clinical practice, male infertility can be broadly divided into two types of reproductive failure: pregestational and gestational infertility [16]. In the present study, nine of our cases were identified as carriers of chromosome 5 translocations, and we also reviewed 106 cases of chromosome 5 translocation reported in the literature. The breakpoints that we identified on chromosome 5 were found to be associated with pregestational or gestational infertility. One case was associated with pregestational infertility and eight cases were related to gestational infertility. Mikelsaar et al. [17] and Venkateshwari et al. [18] reported that the breakpoints at 5q33 and 5q35 in male carriers were associated with infertility. Kim et al. [19] reported that the breakpoint at 5p13 could interfere with spermatogenesis, and that breakpoints at 5q15, 5q21.2, 5q22 and 5q32 were related to recurrent abortion. To study the relationship of these breakpoints on chromosome 5 with male infertility, we analyzed recent published literature and revealed clinical features in carriers of chromosome 5 translocations. The karyotype results and clinical findings at chromosome 5 are summarized in Table 2. A common clinical feature associated with the breakpoints at 5p13, 5q33 and 5q35 was recurrent miscarriage, which was not consistent with the above reports.

Male infertility affects about 50% of couples unable to achieve pregnancy [20]. Chromosomal abnormalities are closely related to male infertility [21], and cytogenetic detection can provide valuable information for genetic counseling of infertile males [22]. Previous reports have shown that infertile men have an 8–10-fold higher prevalence of chromosomal abnormalities than fertile men [19]. Chromosomal translocation alters the complex and vital process of spermatogenesis, and leads to male infertility [20]. Chromosome 5 translocation has often been associated with male infertility or recurrent pregnancy loss [17, 18, 23].

Table 3 shows that all breakpoints were associated with gestational infertility. These cases indicated that such breakpoints were not responsible for pregestational infertility, so another breakpoint of translocation must be responsible in these individuals. For instance, two individuals with the breakpoint 5q22 were associated with pregestational infertility, and exhibited clinical features of oligoasthenoteratozoospermia and asthenozoospermia (case 47 and 102, respectively, Table 2). The corresponding breakpoints of translocation in case 47 and 102 were 8q24.1 and 20p13, respectively. Kott et al. [24] reported that the primary ciliary dyskinesia-19 (CILD19) gene (OMIM: 614,935), mapped to chromosome 8q24, was associated with asthenospermia in infertile men. Previous studies have shown that the sperm flagellar protein 1 (SPEF1) gene (OMIM: 610,674) located on chromosome 20p13 was be associated with curvature of microtubule bundles and the axoneme of sperm flagella [25]. Previous studies suggested that disruptions of CAMK4 located on chromosome 5q22.1, SPINK13 located on

| Breakpoints | Number of patients with pregestational infertility | Number of patients with gestational infertility |
|-------------|---------------------------------------------------|-----------------------------------------------|
| p15.3       | 1                                                 |                                               |
| p15.2       | 3                                                 |                                               |
| p15.1       | 4                                                 |                                               |
| p15         | 11                                                |                                               |
| p14         | 1 5                                               |                                               |
| p13.3       | 3                                                 |                                               |
| p13         | 9                                                 |                                               |
| p12         | 2                                                 |                                               |
| p11         | 1 2                                               |                                               |
| q10         | 1                                                 |                                               |
| q11         | 3                                                 |                                               |
| q11.2       | 2                                                 |                                               |
| q12         | 1                                                 |                                               |
| q13         | 1 9                                               |                                               |
| q13.1       | 1                                                 |                                               |
| q13.2       | 1                                                 |                                               |
| q14         | 1 1                                               |                                               |
| q15         | 1 4                                               |                                               |
| q21         | 4                                                 |                                               |
| q22         | 2 3                                               |                                               |
| q22.1       | 1                                                 |                                               |
| q23.1       | 1                                                 |                                               |
| q23.2       | 1                                                 |                                               |
| q23.3       | 1                                                 |                                               |
| q31         | 2 3                                               |                                               |
| q31.1       | 1                                                 |                                               |
| q33         | 8                                                 |                                               |
| q33.1       | 2                                                 |                                               |
| q33.2       | 1                                                 |                                               |
| q33.3       | 3                                                 |                                               |
| q34         | 2                                                 |                                               |
| q35         | 1 6                                               |                                               |
| q35.1       | 1 2                                               |                                               |
| q35.3       | 2                                                 |                                               |
chromosome5q32 and the testis-specific serine/threonine kinase (TSSK1B) gene mapped to chromosome 5q22.2 were associated with loss of sperm function and human male infertility [8, 9, 26]. In addition, the most common breakpoint, mapped to 5p15, was associated with gestational infertility. Other breakpoints were also identified as being associated with gestational infertility. For those affected by these breakpoints, natural conception remained possible with the potential to have normal children. For example, Ikuma et al. [4] reported that the live birth rate with natural conception for translocation carriers was 65%–83% cumulatively. However, natural conception has a greater risk. The number of chromosomal unbalanced gametes is large, leading to repetitive pregnancy loss, and may have repercussions on the fertility of translocation carriers. For these carriers, informed choice should be provided during genetic counseling.

The major limitation of our present study was the relatively small number of carriers of chromosome 5 translocations. Furthermore, we did not investigate the specific molecular effects of the translocations by molecular-cytogenetic methods.

Conclusions
In the present study, 115 carriers of chromosome 5 translocations were reviewed. The most common translocation and breakpoint were t(4;5) and 5p15, respectively. All breakpoints at chromosome 5 were associated with gestational infertility. In genetic counseling, physicians should consider chromosome 5 and its breakpoints. Carriers of chromosome 5 translocations maybe choose to continue with natural conception or use available assisted reproductive technologies, such as preimplantation genetic diagnosis.

Abbreviations
A2Z: Azosperminia factor; CAMK4: Ca2+/calmodulin-dependent protein kinase IV; CILD19: Ciliary dyskinesia-19; ISCN: International System for Human Cytogenetic Nomenclature; PGD: Preimplantation genetic diagnosis; SPEF1: Sperm flagellar protein 1; Spink13: Serine protease inhibitor, Kazal-type 13; TSSK1B: Testis-specific serine/threonine kinase

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Availability of data and materials
Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

Authors’ contributions
HGZ, LLL and HBJ performed the literature search, analyzed the data and wrote the manuscript. RWW, YP and HZ collected the clinical cases and patients. HGZ and RZL are responsible for the content and writing of the paper. All authors read and approved the final manuscript.

Ethics approval and consent to participate
The study protocol was approved by the Ethics Committee of the First Hospital of Jilin University, and written informed consent was obtained from all participants. (No.2010–082)

Consent for publication
Not applicable

Competing interests
The authors declare that they have no competing interests.

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