A case of congenital toxoplasmosis-associated miscarriage with maternal infection four months prior to conception

Loïc Simon, Cynthia Trastour, Albert Soler, Fabienne Jeannet, Marie-Fleur Durieux, Karine Passebosc-Faure, Pierre Marty, Christelle Pomares

A case of congenital toxoplasmosis-associated miscarriage with maternal infection four months prior to conception.

Loïc Simon[a,b*], Cynthia Trastour[c], Albert Soler[d], Fabienne Jeannet[e], Marie-Fleur Durieux[f,g], Karine Passebosc-Faure[f], Pierre Marty[a,b], Christelle Pomares[a,b].

a- Service de Parasitologie-Mycologie, CHU de Nice, Université Côte d'Azur, Nice, France

b- Inserm U1065, C3M, Nice, France

c- Service de Gynécologie-Obstétrique, CHU de Nice, Nice, France

d- Polyclinique Saint-Jean, Cagnes-sur-Mer, France

e- Médecine générale, Saint-Laurent-Du-Var, France

f- Centre National de Référence Toxoplasmose / *Toxoplasma* Biological Resource Center, CHU Limoges, Limoges, France

g- Inserm UMR_S 1094, Neuroépidémiologie Tropicale, Laboratoire de Parasitologie-Mycologie, Faculté de Médecine, Université de Limoges, Limoges, France

Word count: 1367 ; Figure count: 1 ; Table count: 1

Short title: Maternal toxoplasmosis before conception

* Corresponding author:

Loïc Simon (email: simon.l@chu-nice.fr, tel: +33 (0)4 92 03 62 54)

Service de Parasitologie-Mycologie, CHU de Nice - Hôpital l'Archet, 151 route Saint-Antoine de Ginestière, CS 23079, 06202 Nice cedex 3, France.

Disclosure: The authors have no competing interests and no financial support or funding to declare.

ABSTRACT

Background: We report a case of fatal congenital toxoplasmosis with maternal infection dated four months before pregnancy in the absence of any specific immunosuppressive condition.

Case: Ms. D. experienced submaxillary lymphadenitis in February 2018. The medical workup performed revealed an acute *T. gondii* infection. She became pregnant in June 2018 while she still had adenopathy. The second obstetrical ultrasound, performed at 16 weeks of pregnancy, revealed a fetal death. The research for *T. gondii* by PCR was positive in the products of conception.

Conclusion: Diagnosis of toxoplasmosis should be discussed in case of miscarriage with lymphadenitis. As lymph nodes in *T. gondii* infection could be responsible for iterative release of parasites and fetal death, symptomatic toxoplasmosis should be treated in women of childbearing age.

Keywords: *Toxoplasma gondii,* congenital toxoplasmosis, preconception, miscarriage, fetal death.

CASE REPORT

The intracellular parasite *Toxoplasma gondii* is responsible for toxoplasmosis, whose primary infection is asymptomatic in about 80% of cases in healthy people. Sometimes, mild symptoms may be present, including asthenia, cervical lymphadenitis, fever and biological mononucleosis syndrome. Newborns are at risk of congenital toxoplasmosis when the infection occurs during pregnancy. The tachyzoite form of the parasite can then be transmitted to the fetus by random breaks from placental foci. The risk of transmission is considered low when the maternal infection occurs at the beginning of pregnancy but it increases up to 70% at the end of pregnancy [1]. Conversely, severity of congenital infection is higher at the beginning compared to the end of pregnancy. Few congenital infections are described when women were infected before the date of conception. In the majority of cases, these infections can be explained by reactivation of a past infection during pregnancy in immunocompromised mothers [2]. Here, we report a case of fatal congenital toxoplasmosis with maternal infection dated four months before pregnancy in the absence of any specific immunosuppressive condition.

In February 2018, Ms. D., a 28-year-old G1P1 with no medical conditions and no foreign travel, presented with fatigue and enlarged cervical lymph nodes. After an evaluation by general physicians and ENT specialists, she was diagnosed with submaxillary lymphadenitis, confirmed by a cervical ultrasound. The biological workup, including a complete blood count with differential, was normal and did not show obvious sign of immunosuppression. The cytomegalovirus, Epstein-Barr Virus, Hepatitis B and C Virus, and HIV serological tests results were negative and rubella serology demonstrated immunity. As the lymphadenitis persisted, a *T. gondii* serology was performed the 4th of April and was consistent with an acute infection dated beginning of February with presence of specific IgG, IgM and IgA (**Table 1**). IgG avidity was low, which was not relevant in helping to assume the age of the infection, as only high-avidity anti-*Toxoplasma* IgG antibodies is informative to exclude acute infection in the preceding 4 months. The last known negative *T. gondii* serology dated November 29, 2017: IgG = < 0.5 UI/mL; IgM index = 0.37 (ADVIA Centaur® Toxo Assay). An ophthalmologic exam did not reveal any abnormality. No treatment was prescribed at that time.

Few months later, Ms. D. became pregnant. The first day of the last menstrual period was May 22, 2018 and the estimated date of conception was June 05, 2018. The first fetal ultrasound performed on August 17 during the first trimester demonstrated an embryo with a crown-rump length of 63.8 mm, consistent with a gestational age of 12 weeks and 4 days. All biometric measurements were between the 10th and the 90th percentiles and no morphological abnormalities were observed. On September 12, at 16 weeks and 2 days of pregnancy, a second

obstetrical ultrasound highlighted fetal death that probably occurred few days after the first ultrasound according to the obstetrical measurements. Uterine curettage was performed the following day at the teaching hospital of Nice, France. Analysis of the products of conception by the laboratory of Parasitology-Mycology revealed a positive *T. gondii* PCR. Microsatellite genotyping performed on the PCR products by the National Reference Center for Toxoplasmosis, in Limoges, found a Type II *T. gondii* strain (TgH 23069A). Type II strains represent 95% of the circulating strains in France [3–5]. *Toxoplasma gondii* PCR performed on the peripheral blood of Ms. D. was negative. **Figure 1** summarizes the timeline of the events. After questioning Ms. D., we learned that the submaxillary lymphadenitis was still palpable when she became pregnant and during the pregnancy. To date, Ms. D. is doing well. She became pregnant again on April 2019 and gave birth to a healthy baby on December 31.

In some countries like France, pregnant women are tested in the early weeks of gestation for the presence of specific IgG and IgM against *T. gondii*. When the first serology is negative, a monthly prenatal screening is performed. This approach allows prompt initiation of treatment of the mothers who seroconvert and of infected fetuses along with being cost-effective [1,6]. In our case, *T. gondii* infection, proven by the association of symptomatology and specific serology, occurred four months before conception. Per protocol, no further treatment or evaluation was performed and there should have been no consequences on the pregnancy. *Toxoplasma gondii* was transmitted to the fetus long after the estimated date of infection. Similar cases are rare in the literature and to our knowledge, this is the first description of proven fetus infection with such a long period of time between mother infection and conception [2,7–14]. The presence of enlarged cervical lymph nodes seems to be the common feature in similar situations of pregnant women without immunosuppressive pathology [7,10–12]. We might wonder if an iterative release of parasites from the lymph nodes may have been responsible, in our case and the others, for fetus infection. Moreover, when primary infection is symptomatic, there could be a prolonged parasitemia, promoting transmission to the fetus. Our patient was not treated at the time of diagnostic but treatment with spiramycin before conception have been performed in other cases and failed to prevent infection of the fetus [2,7,8,11]. Currently, there are no official recommendations about the preconceptional toxoplasmosis care. We agree with Villena *et al.* [7] on advocating a pregnancy-free interval of at least six months after proven toxoplasmosis infection. In addition, specific monitoring, by regular ultrasound and prenatal diagnosis, in pregnant immune women with adenopathy should be recommended. Effective treatment of symptomatic toxoplasmosis in women with a desire for pregnancy could be advisable too. Treatment strategy with trimethoprim-sulfamethoxazole (already used for *T. gondii* infection in

immunocompromised patients) could be a good alternative to spiramycin. A double-blind, randomized clinical trial by Alavi *et al.* [15] showed the benefits of a treatment by trimethoprim-sulfamethoxazole (= cotrimoxazole) at 48 mg/kg/day for 1 month on the healing of lymphadenitis and the decrease of anti-*T. gondii* IgM level. Moreover, it is also important to encourage practitioners to examine women with miscarriage for the presence of enlarged lymph nodes. In case of lymphadenitis, the diagnosis of toxoplasmosis should be discussed. The role of *T. gondii* in unexplained miscarriages has been rarely assessed and is probably underestimated. According to the review by Giakoumelou *et al*. [16], the link between miscarriages and congenital toxoplasmosis was poorly studied. In this review, the study populations ranged from 100 to 326 women with a history of miscarriage. The analyses performed were often limited to serological tests or *T. gondii* PCR in mothers' blood and these assays are not those which make it possible to diagnose a congenital toxoplasmosis. Prevalence of toxoplasmosis ranges from 20% to 70% worldwide and more powerful studies about the potential role of *T. gondii* in miscarriages are needed to better prevent fetus infection.

This case report highlights the fact that a symptomatic acute infection by *T. gondii* should be considered differently than an asymptomatic one. A period of six months should be considered between the symptomatic infection and the pregnancy, in order to prevent unexplained miscarriage.

131 REFERENCES

132 [1] Wallon M, Peyron F, Cornu C, Vinault S, Abrahamowicz M, Kopp CB, Binquet C. Congenital
133 *Toxoplasma* Infection: Monthly Prenatal Screening Decreases Transmission Rate and Improves Clinical
134 Outcome at Age 3 Years. Clin Infect Dis. 2013;56(9):1223–31.

135 [2] Marty P, Bongain A, Rahal A, Thulliez P, Wasfi D, Lambert JC, Le Fichoux Y, Gillet JY. Prenatal
136 diagnosis of severe fetal toxoplasmosis as a result of toxoplasmic reactivation in an HIV-1 seropositive
137 woman. Prenat Diagn. 1994;14(5):414–5.

138 [3] Ajzenberg D, Collinet F, Aubert D, Villena I, Dardé M-L, French ToxoBs network group, Devillard S.
139 The rural-urban effect on spatial genetic structure of type II *Toxoplasma gondii* strains involved in human
140 congenital toxoplasmosis, France, 2002-2009. Infect Genet Evol. 2015;36:511–6.

141 [4] Aubert D, Ajzenberg D, Richomme C, Gilot-Fromont E, Terrier ME, de Gevigney C, Game Y, Maillard
142 D, Gibert P, Dardé ML, Villena I. Molecular and biological characteristics of *Toxoplasma gondii* isolates
143 from wildlife in France. Veterinary Parasitology. 2010;171(3):346–9.

144 [5] Halos L, Thébault A, Aubert D, Thomas M, Perret C, Geers R, Alliot A, Escotte-Binet S, Ajzenberg D,
145 Dardé M-L, Durand B, Boireau P, Villena I. An innovative survey underlining the significant level of
146 contamination by *Toxoplasma gondii* of ovine meat consumed in France. International Journal for
147 Parasitology. 2010;40(2):193–200.

148 [6] Binquet C, Lejeune C, Seror V, Peyron F, Bertaux A-C, Scemama O, Quantin C, Béjean S, Stillwaggon E,
149 Wallon M. The cost-effectiveness of neonatal versus prenatal screening for congenital toxoplasmosis.
150 PLoS ONE. 2019;14(9):e0221709.

151 [7] Villena I, Chemla C, Quereux C, Dupouy D, Leroux B, Foudrinier F, Pinon J. Prenatal diagnosis of
152 congenital toxoplasmosis transmitted by an immunocompetent woman infected before conception. Reims
153 Toxoplasmosis Group. Prenatal diagnosis. 1998;18:1079–81.

154 [8] Dollfus H, Dureau P, Hennequin C, Uteza Y, Bron A, Dufier JL. Congenital *toxoplasma* chorioretinitis
155 transmitted by preconceptionally immune women. Br J Ophthalmol. 1998;82(12):1444–5.

[9] Pons JC, Sigrand C, Grangeot-Keros L, Frydman R, Thulliez P. [Congenital toxoplasmosis: transmission to the fetus of a pre-pregnancy maternal infection]. Presse Med. 1995;24(3):179–82.

[10] Desmonts G, Couvreur J, Thulliez P. [Congenital toxoplasmosis. 5 cases of mother-to-child transmission of pre-pregnancy infection]. Presse Med. 1990;19(31):1445–9.

[11] Boumahni B, Randrianivo H, Flodrops H, Kauffmann E, Sauve F, Chauvet O, Renouil M, Fourmaintraux A. [Maternal toxoplasmosis before conception and chorioretinitis in twin sisters]. J Gynecol Obstet Biol Reprod (Paris). 2004;33(3):248–50.

[12] Vogel N, Kirisits M, Michael E, Bach H, Hostetter M, Boyer K, Simpson R, Holfels E, Hopkins J, Mack D, Mets MB, Swisher CN, Patel D, Roizen N, Stein L, Stein M, Withers S, Mui E, Egwuagu C, Remington J, Dorfman R, McLeod R. Congenital toxoplasmosis transmitted from an immunologically competent mother infected before conception. Clin Infect Dis. 1996;23(5):1055–60.

[13] Marty P, Le Fichoux Y, Deville A, Forest H. [Congenital toxoplasmosis and preconceptional maternal ganglionic toxoplasmosis]. Presse Med. 1991;20(8):387.

[14] Chemla C, Villena I, Aubert D, Hornoy P, Dupouy D, Leroux B, Bory JP, Pinon JM. Preconception seroconversion and maternal seronegativity at delivery do not rule out the risk of congenital toxoplasmosis. Clin Diagn Lab Immunol. 2002;9(2):489–90.

[15] Alavi SM, Alavi L. Treatment of toxoplasmic lymphadenitis with co-trimoxazole: double-blind, randomized clinical trial. Int J Infect Dis. 2010;14 Suppl 3:e67-69.

[16] Giakoumelou S, Wheelhouse N, Cuschieri K, Entrican G, Howie SEM, Horne AW. The role of infection in miscarriage. Hum Reprod Update. 2016;22(1):116–33.

181 TABLE

Table 1. Biological results

Assay performed	11/29/2017	04/04/2018	08/18/2018	09/07/2018	09/13/2018	09/24/2018	11/14/2018
IgG (IU/mL)	< 0.5 [a]	194.9	732.3	1362.3	n/a	1350.9	1096.2
IgG avidity	n/a	5.04%	38.10%	n/a	n/a	n/a	n/a
IgM (index)	0.37 [b]	15.38	4.74	3.04	n/a	3.87	5.01
IgA (index)	n/a	4.2	3	n/a	n/a	n/a	n/a
PCR (products of conception)	n/a	n/a	n/a	n/a	Positive	n/a	n/a
PCR (patient's blood)	n/a	n/a	n/a	n/a	n/a	Negative	n/a

IgG (Architect®, Abbott Laboratories): negative < 1.6 ; equivocal 1.6 - 2.9 ; positive ≥ 3

IgG avidity (Architect®, Abbott Laboratories): ≥ 60% → past infection > 4 months ago

IgM (Architect®, Abbott Laboratories): negative < 0.50 ; equivocal 0.50 - 0.59 ; positive ≥ 0.60

IgA (Platelia™, Bio-Rad): negative < 0.8 ; equivocal 0.8 - 1 ; positive ≥ 1

[a] **IgG** (ADVIA Centaur®, Siemens): negative < 6.4 ; equivocal 6.4 - 9.9 ; positive ≥ 10

[b] **IgM** (ADVIA Centaur®, Siemens): negative < 0.9 ; equivocal 0.90 - 0.99 ; positive ≥ 1

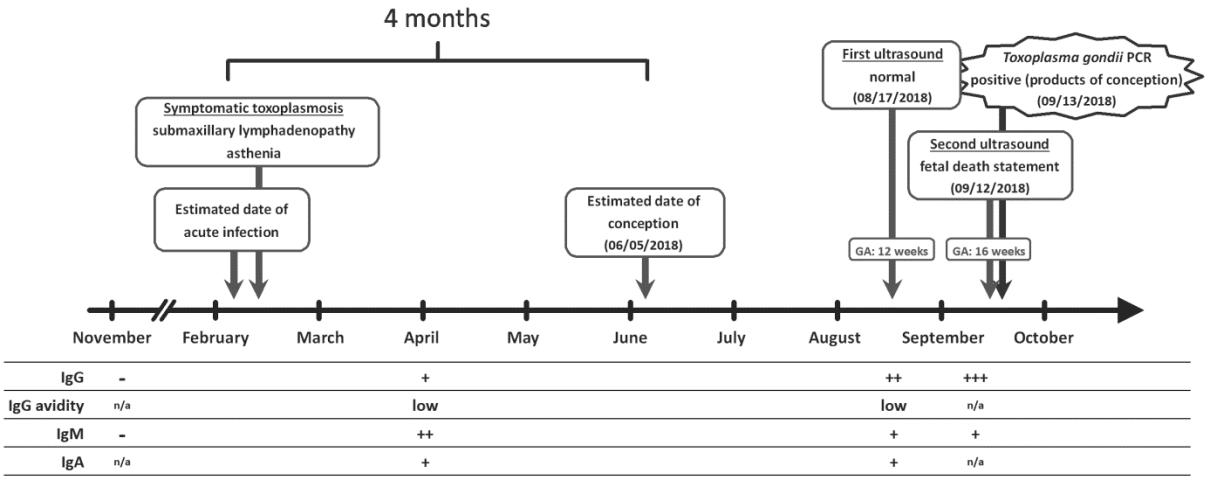
n/a: not available

182

183

184

185 FIGURE



186

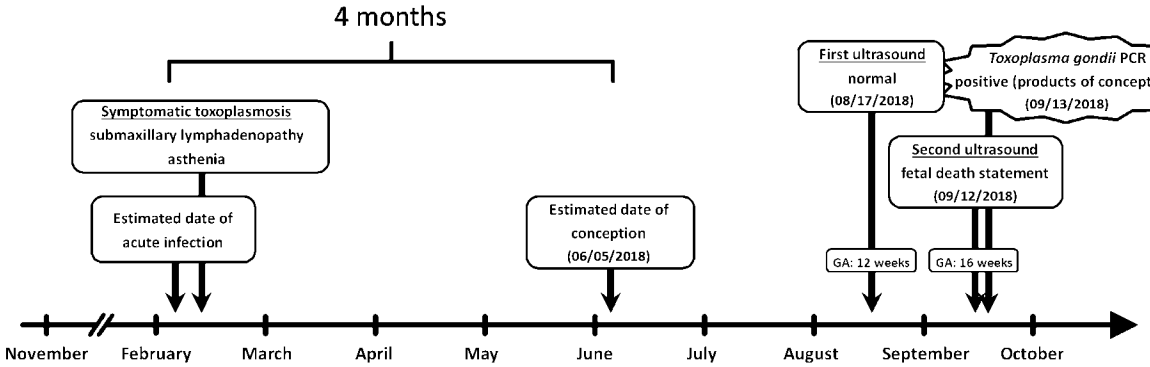
187 **Figure 1:** Timeline of the events and important serological findings

188

LEGENDS

Table 1: Biological results

Figure 1: Timeline of the events and important serological findings (serological results are expressed qualitatively according to the cut-offs of the tests described in Table 1; GA: Gestational age; n/a: not available)



IgG	-	+	++	+++	
IgG avidity	n/a	low	low	n/a	
IgM	-	++	+	+	
IgA	n/a	+	+	n/a	