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CASE DISCUSSION

Comment to the case: Successful pregnancy in a severely hypoxemic patient with alveolar proteinosis

Discussão de caso clínico: Gravidez de termo em doente com proteinose alveolar e insu ciência respiratória grave

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Pulmonary alveolar proteinosis (PAP) is a rare disease. The true prevalence is probably unknown with a recent Japanese study suggesting 6-7 per million in the general population.[1]

Different forms of alveolar proteinosis exist: *a)* PAP due to impaired GM-CSF signaling –comprising the autoimmune/common PAP and the diseases associated with GM-CSF receptor and -chain deficiency; *b)* PAP due to another underlying clinical disorder –secondary PAP; *c)* genetic disorders of surfactant production –surfactant protein B de ciency, surfactant protein C dysfunction and ABCA3 dysfunction.

Autoimmune pulmonary alveolar proteinosis is the commonest form of PAP accounting for 90%of the cases.

Pulmonary alveolar proteinosis is now considered an autoimmune disorder because high levels of polyclonal, neutralizing GM-CSF auto antibodies are specifically associated with this form of disease. GM-CSF is critical for alveolar macrophage terminal differentiation and immune functions, pulmonary surfactant homeostasis, and lung host defense. Autoantibody levels do not correlate with disease severity.

The disease occurs predominantly in males with a male: female ratio of ~3:1. The peak age of onset is 30-50 years and it occurs predominantly in smokers and individuals with ill-de ned pulmonary exposures.

Diagnosis is often delayed, 1/3 of the patients in the Japanese study were diagnosed on routine chest radiographs, so asymptomatic. The natural history may be of spontaneous improvement, persistent, unremitting symptoms, or progressive deterioration with respiratory failure. Spontaneous remission is believed to occur in 1/3 of patients. Until recently whole lung lavage (WLL) was the sole existing treatment. It is safe, well tolerated and provides long-lasting bene ts when performed by trained personnel.[2,8] WLL seems to have changed the natural history of this disease. In the experience of the Royal Brompton Hospital of London all patients obtained full remission of PAP. In the series of Beccaria 70%of patients were free from recurrent manifestations of PAP 3 years after WLL. More recently treatment with recombinant GM-CSF either aerosolized or subcutaneous has been used and the results have been presented in small clinical trials.[1] 50-30%of patients respond to this form of treatment. The optimal dose, timing and route of administration or duration of therapy is not standardized nor de ned. It is an expensive treatment but it might be of value in a setting where WLL

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is not easily available or when there is a contraindication to general anesthesia.

When it comes to rare diseases it is often very dif cult to decide practical matters like advising for or against a planned pregnancy. The literature data are scarce especially if we note that besides being a rare disease there is a preponderance of males with PAP. This is why the paper by Belchior at al[3] is so very much welcome. When it comes to decision regarding rare diseases, published clinical cases are usually the only available source of help.

The 44 y.o patient addressed in their paper was diagnosed as having PAP two years before this pregnancy and had had WLL once. She had seven previous pregnancies with no history of pulmonary disease and I wonder if PAP might have already been there at some time. Due to symptomatic disease and a PaO_2 of 53 mmHg a sequential WLL was performed at week 8 of gestation, with an increase of PaO_2 to 83 mmHg. This permitted a near normal pregnancy and delivery at 37 weeks by cesarean section. There was no danger either to mother or child.

Matuschack et al[7] presented a case of a 23 y.o. female with known PAP who had also had a previous twin gestation complicated with hypoxemia (53 mmHg); there was no intervention at that time and she had a vaginal delivery of two low birth-weight infants; at 32 weeks of this second gestation a sequential WLL was done with amelioration of PaO_2 from 52 mmHg to 64 mmHg allowing a full-term vaginal delivery and a healthy infant. There were no complications from WLL.

Canto et al[6] published the case of 19 y.o. women with familial PAP with mild restrictive disease that delivered a healthy baby at 32 weeks and 6 days by vaginal delivery. Pulmonary function remained unchanged throughout pregnancy and no intervention was needed.

Crocker et al[5] described a 29 y.o. female diagnosed as having PAP in the course of a 33 week pregnancy, presenting with acute respiratory distress and a resting PaO_2 of 45 mmHg. A cesarean section was performed, the diagnosis established by bronchoalveolar lavage and 14 WLL were needed before a normal lung function was attained. The baby was transferred to a neonatal intensive care unit with a diagnosis of hyaline membrane disease.

Huisman et al[4] in a Dutch paper refer to a PAP patient treated with recombinant Gm-CSF which was suspended and resumed after parturition. A cesarean section was performed.

At a National Congress we presented a 38 y.o. female (unpublished data) who had had an ongoing history of PAP for 19 years, treated with 15 WLL and mild restrictive lung disease. When she decided to attempt pregnancy two elective sequential WLL were done in order to get her in the very best condition. At week 25 a slight dessaturation on effort was noted (88-89%saturation) and she was put under oxygen therapy. At that time WLL was considered but we felt that it would do more harm than good. From 28 week on her exercise O_2 saturation increased to 90%and remained as so until delivery. She continued on oxygen therapy. A cesarean section was performed at 38 weeks and 6 days, a healthy baby was born. PaO_2 during delivery was 52 mmHg and 12 hours after delivery went up to 79.8 mmHg. After this rst pregnancy she did not need any additional WLL, lung CT features got better. Two years later she decided to become pregnant again. As the disease was stable with no need of WLL or hypoxemia on effort we decided not to perform prophylactic WLL. A healthy full term baby was born by cesarean section. Pregnancy was uneventful with no need of oxygen supplementation.

From the cases presented above one may conclude that it is possible that a successful outcome can be achieved for both mother and child in pregnant patients with PAP. Also, WLL was performed at 8 weeks and 33 weeks gestation with no apparent harm either to the mother or the fetus. Despite restrictive lung disease and hypoxemia some patients do not need any intervention. Ideally in a known PAP patient pregnancy should be planned to optimize the best functional context, if needed an elective WLL (or recombinant GM-CSF therapy) could be advised before pregnancy is attempted. Some obstetricians experienced in pregnancy in a context of hypoxemic diseases would not consider intervening unless O_2 saturation could not be kept above 80%. Also, at this point we don't have much information about the effect of therapeutic GM-CSF on maternal and fetal well-being –though the evidence suggests that it may be GMCSF deficiency that we have to worry about as there is some evidence of signi cantly reduced blood concentrations in unexplained recurrent abortion.[9] It might be an appealing resource to use in a pregnant patient too ill to undergo WLL.

So, many questions remain unanswered in this fascinating disease. It is from my point of view very useful for us, clinicians, that Medline searchable journals accept this type of clinical case. Although the results of prospective clinical studies are doubtless the stars of medical research, for rare diseases the study of published clinical cases is still invaluable.

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