Effect Of Obstruction To Sperm Egress On The Male Testis And Epididymis

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Citation

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Abstract

Objective: The effects of obstructive azoospermia on the testis and epididymis have been studied in vasectomized subjects. However, effects of obstruction to sperm egress in primary obstructive azoospermia on the testes and epididymis have not been extensively reported. The present study on fifty patients of primary obstructive azoospermia focuses on the local immune response and its effect on the testis and epididymis. This was a prospective study in a tertiary hospital setting comparing epididymal histology and epididymal fluid antisperm antibody in men with primary obstructive infertility with those in men with proven fertility.

Material and Methods: Fifty males with primary obstructive infertility in the study group and ten subjects with proven fertility as controls were included in the study. While performing vasoepididymostomy on such patients, testicular and epididymal tissues were taken, and epididymal fluid was aspirated for estimation of antisperm antibodies. Testicular and epididymal histologies were studied under light microscopy for evidence of cellular immune response to obstruction. Antisperm antibodies in epididymal fluid were assayed by ELISA.

Result(s): No effects of obstruction were evident on spermatogenesis or the testicular histology. Epididymal epithelial flattening with local or diffuse loss of cilia (n=25); pigment in the epithelial cells as a remnant of sperm ingestion (n=20); intraductal macrophages (n=29) with sperm ingestion in 62%; breach of epithelium with sperm extravasation (n=20) were considered as evidence of effects of obstruction leading to proximal ductal dilatation and damage. Presence of plasma cells and lymphocytes (n=31) and macrophages (n=11) in the interstitium were considered effects of antigenic sperm extravasation in the interstitium. These effects could be a local cell mediated immune response. Significant ELISA for antisperm antibodies was found in 29 patients; all patients with inflammatory cell infiltrate in the interstitium had significant ELISA for antisperm antibodies in the epididymal fluid. The cellular immune response as assessed by the presence of interstitial inflammatory cells and macrophages in epididymal histology was found in 12/20 patients. Testicular biopsies in all patients were normal. Humoral immune response as assessed by significant titres of antisperm antibodies in epididymal fluid was found in 14/20 patients. Evidence of local immune response (cellular or humoral or both) was found in 17/20 patients.

Conclusion(s): We believe that intermittent exposure to small amounts of extravasated sperms in the epididymal interstitium would be sufficient to produce a local cell mediated immune response with its attendant effects on the epididymis, the primary site of sperm maturation, producing irreversible changes in its structure.

INTRODUCTION

The effect of obstruction to the egress of sperms on the testes has been widely studied on vasectomized animal models.[1] Autoimmune orchitis ultimately leading to testicular atrophy and necrosis has also been described.[2,3] In a study of testicular biopsies in various causes of male infertility it was found that regardless of the cause, obstruction of the vas deferens or epididymis per se has no adverse effect on the germinal epithelium or Leydig cells.[4] Silber has correlated the failure of vasectomy reversal with the length of time between vasectomy and reversal and has postulated that in some patients, raised post-operative intra-vasal pressure can over many years lead to permanent damage to the seminiferous tubules.[5] Rajalakshmi et al observed a high percentage of spermatozoa with morphological abnormalities in the ejaculate of men who had undergone vasoepididymostomy to surgically remove epididymal obstruction.[6] They postulated that these abnormalities may be a consequence of severe stress on the testis due to defective absorption of testicular fluid by the obstructed epididymis and the resultant pressure effect caused by fluid circulation.[6]

The epididymis is the site of maximal breakdown and resorption of unejaculated sperms, in addition to its function of sperm storage and maturation. As spermatozoa are still produced and transported along the tract in obstructed infertility, the crucial question concerns the fate of these spermatozoa with new mechanisms for their disposal being activated which can lead to local physiological and immunological changes. Alterations in histology of the epididymis as a consequence of long-term obstruction have been reported earlier.[7,8,9,10] Since similar findings have been reported in epididymal histology taken at the time of vasectomy reversal in males with high antisperm antibody titres[11] and in animals[12,13], it is possible that these changes result from cell mediated immune response. However, this aspect has not been studied.

The testis is an immunologically privileged organ with myoid and Sertoli cells providing the morphological component of the blood-testis barrier such that the highly antigenic sperms do not come in contact with the immunocompetent cells present in the interstitial spaces between seminiferous tubules.[14] On the other hand, the epididymis has intraductal lymphocytes and macrophages and is considered to be the most likely source of antibody secretion and cellular immunity and autoimmunity in the male reproductive tract.[14] The impact of impaired epididymal integrity on autoimmune processes and infertility has been widely recognized.[15] Antisperm antibodies (ASA) may result in the serum, seminal fluid or on sperm surface either as a result of transport of spermatozoal degradation products by the macrophages to the regional lymph nodes, breakdown of the blood-testis / blood-epididymis barrier due to trauma or infection with escape of sperm antigens directly into the microcirculation, or, by production of antibodies against infective agents like Chlamydia which cross react with spermatozoa.[16] It is also possible that in obstructive infertility breach in the epithelium causes extravasation of sperms into the interstitium and brings them in contact with the immunocompetent cells in insufficient amounts to induce detectable ASA. However, repeated exposure to the antigenic sperms may induce a local cell mediated immune response which may be responsible for the histological changes reported in the epididymis.[8,10]

The present study examines the histologic changes in the testis and epididymis of males with primary obstructive infertility in an effort to correlate it with the possibly associated cell mediated immune response to extravasated sperms in the epididymal interstitium.

MATERIALS AND METHODS

Fifty patients of primary obstructive infertility were studied. None of these patients had any history or clinical evidence of infection or trauma. Clinical findings were recorded in a pre-determined proforma. These patients were subjected to semen analysis (including presence/absence of fructose), fine needle aspiration cytology (FNAC) of both testes, serum antisperm antibody and serum FSH, LH and testosterone. The cytologic material obtained was smeared, air dried and stained with the May Grunwald Giemsa method. The cells were classified according to morphological criteria described by Schenck and Schill and adapted with modification.[17] By studying the proportion of Sertoli cells versus spermatogenetic cells, it was possible to give a cytological diagnosis in histological terms by the semiquatitative analysis such that four standard patterns could be recognized (grade 1 or normal spermatogenesis; grade 2 or hypospermatogenesis; grade 3 or maturation arrest and grade 4 or Sertoli cell only syndrome).Only primary infertility cases showing active spermatogenesis on FNAC of the testes and with a clinically palpable epididymis and serum FSH levels ≤ 2½ times normal were included in the study.

However, during the course of our study, certain criteria were relaxed. Some patients with FNAC of testis showing impaired spermatogenesis were also selected for our study. Four patients with FSH value more than 2.5 times normal were also included because two patients showed normal spermatogenesis on FNAC of testes while the other two patients with hypospermatogenesis on FNAC insisted for surgery despite the prognosis explained to them. Six patients with bilateral absence of vas deferens were also included in our study because of our policy to confirm absence of vas by scrotal exploration and also because we routinely form an artificial spermatocele in these patients to give them a chance for utilizing one of the cheaper methods of assisted reproduction, i.e. intra-uterine insemination of aspirated sperms.

Testicular exploration was effected under local anaesthesia. The size and consistency of the testis were noted. Epididymis was identified and its features noted — distension, appearance and amount of discharge on incision over epididymis.

Patency of the vas was confirmed. The epididymis was incised preferably at the site of maximal distension as evident from the yellowish inspissated contents and the character of the fluid coming out of the epididymis was

noted and smears of this fluid were made for observing sperm morphology. Fluid was also taken in a syringe diluted with normal saline for determination of anti-sperm antibodies. If the vas was present a single layer side-to-side vasoepididymal anastomosis was performed. The exploration was completed after taking a testicular biopsy which included part of tunica albuginea. Testicular and epididymal tissues were preserved in formalin (for histopathology) and glutaraldehyde (for electron microscopy) along with smears of epididymal fluid. The epididymal fluid was centrifuged and the supernatant was stored at -20° C for analysis of antisperm antibody by ELISA. The sediment was made into pellets for study of sperm morphology.

Ten controls were also studied. They were of proven fertility. Testicular biopsy and epididymal wedge biopsy were taken at the time of autopsy or from patients who underwent orchiectomy for any reason except for testicular torsion or testicular malignancy. Epididymal fluid was also aspirated for cytology for sperm morphology and also for analysis of antisperm antibodies.

Grade of spermatogenesis in the testicular tissue was done according to established norms.[18] Leydig cells were reported as normal or hyperplasia and the basement membrane was notes as normal or thickened. The interstitiurn was reported for presence of lymphocytes, plasma cells, histiocytes. Quantitation of mature spermatids per tubule was totaled in twenty tubules and the total was divided by twenty to give an estimate of number of mature spermatids per tubule.[19]

The features observed in epididymal tissue were the ducts whether normal or dilated and their contents (macrophages, sperms, desquamated epithelial cells) were recorded. Epithelial flattening or breach and lining cells (cilia, pigment, nuclei, sperm ingestion) were specifically reported. Intraductal macrophages were examined for vacuolation, sperm ingestion and pigment. The interstitium was reported for extravasation of sperm (with or without epithelial breach), macrophages (with or without pigment) and infiltration (lymphocytes, plasma cells). The cells were identified by their morphological characteristics and by immunohistochemistry.

ELISA technique was used to detect antisperm antibodies by utilizing a commercially available kit. The kit is an indirect noncompetitive enzyme immunoassay for the semiquantitative and qualitative determination of antibodies directed to spermatozoa surface antigen. The wells of a microtiter plate are coated with spermatozoa surface antigen. Antibodies specific for sperm present in the patient sample bind to the antigen. In a second step the antigen-antibody complex reacts with an enzyme labeled second antibody (Enzyme Conjugate) which leads to the formation of an enzyme labeled antigen-antibody sandwich complex. The enzyme label converts added substrate to form a colored solution. The rate of color formation from the chromogen is a function of enzyme conjugate complexed with the bound antibody and thus is proportional to the initial concentration of the respective antibodies in the patient sample. The detection limit of the assay is 0.2 U/ml and permits the determination of lgG, IgM and lgA antibodies directed against sperm surface antigens.

The Chi square test was used for statistical analysis with Yates modification wherever applicable.

OBSERVATIONS

Fifty four percent of the patients were > 30 years old at presentation (mean: 30.3 yrs.; median: 30 yrs.; range: 23 – 49 yrs.) If older age were to be taken as a poor prognostic indicator for outcome of the treatment, then this would be an important prognostic factor in our study group. 46/50 patients had FSH value < 20 and 35 /46 of these patients had a grade I spermatogenesis. This was found to be statistically significant ($p < 0.05$).

Figure 1

	<8	8-20	>20
Gr. 1	27	8	2
Gr. 2	3	3	0
Gr. 3	2	1	1
Gr. 4	0	2	1

At operation, epididymal distension correlated well with discharge on cutting the epididymis. (Table 1) Thus, all the nine patients who did not have discharge on cutting the epididymis, did not have distended epididymis although 9/15 patients without a distended epididymis still had discharge on cutting the epididymis (1+ in 7 patients and 2+ in 2 patients). All patients with distended epididymis had 1+ to 3+ discharge on cutting the epididymis. However, the post

operative period is too short to assess the effect of these findings on the outcome of the surgery.

Testicular histology in both the patient and the control group was unremarkable. There was no thickening of the basal membrane, inflammatory cell (lymphocyte, plasma cell or macrophage) infiltration or any evidence of fibrosis. Quantitative testicular biopsy, i.e., number of mature spermatids per tubule, which is very useful in predicting what the post operative sperm count should be in patients of obstructive infertility, in the present study revealed that 33 / 50 (66%) patients had > 30 spermatids per tubule and all these patients had Grade I spermatogenesis on testicular biopsy ($p < 0.001$).

Three patients had significant levels of antisperm antibody levels in the serum. However, only one of these patients had positive ELISA for antisperm antibodies in the epididymal fluid. On the other hand, 28 out of 47 patients with absence of antisperm bodies in blood had a significant ELISA in the epididymal fluid. This finding was not found to be statistically significant ELISA. Amongst the cases with inflammatory lymphocytic infiltration, 100% of the cases in whom epididymal fluid could be obtained had significant ELISA.

Figure 2

Features in epididymal histology	No (n=20) [%]	
Epithelial flattening with loss of cilia	25 [50]	Fig. 1
Pigment in epithelial cells	20 [20]	Fig. 2
Ductal dilatation	31 [62]	Fig. 3
Ductal sperms	33 [66]	Fig. 3
Ductal macrophages	29 [58]	Fig. 4
Vacuolation	25 [86.2]	
Sperm ingestion	18 [62.1]	Fig.4
Pigment	09 [31.0]	Fig. 5
Epithelial breach with sperm extravasation	20 [40]	Fig. 5
Interstitial macrophages	11 [22]	Fig. 6
Interstitial lymphocytes, plasma cells etc	31 [62]	Fig. 6

Changes in epididymal histology due to obstruction to sperm egress (Table 2): Epithelial flattening with loss of cilia (focal or diffuse) was observed in 50% of the cases. Though sperm ingestion by the lining epithelial cells could not be demonstrated, pigment as present in the epithelial cells in 20 cases. Dilatation of the epididymal ducts was present in 62% of the cases. Sperms in varying density within the epididymal ducts were present in 66% of the cases and macrophages within the

Figure 3

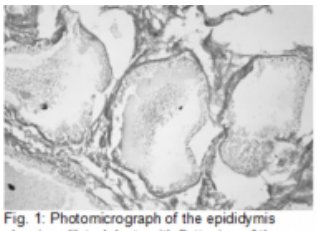

Fig. 1: Photomicrograph of the epididymis showing dilated ducts with flattening of the epithelium and presence of pigment (H&E x100)

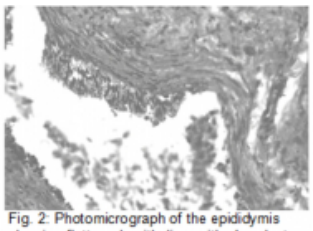

Fig. 2: Photomicrograph of the epididymis showing flattened epithelium with abundant pigment in epithelial cells and dense peritubular fibrosis. (H&E x400)

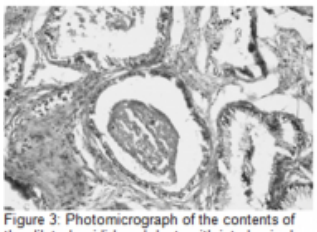

Figure 3: Photomicrograph of the contents of the dilated epididymal ducts with intraluminal sperms and pigment in the cells. (H&E x200)

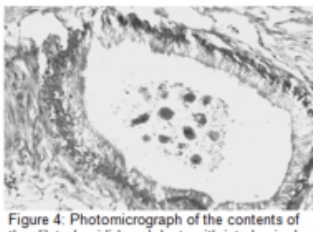

Figure 4: Photomicrograph of the contents of the dilated epididymal ducts with intraluminal and interstitial macrophages. (H&E x400)

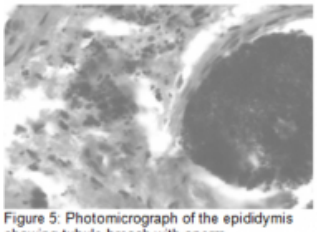

Figure 5: Photomicrograph of the epididymis showing tubule breach with sperm extravasation with pigment laden macrophages (H&E x600)

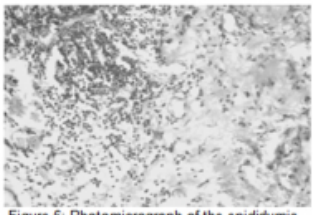

Figure 6: Photomicrograph of the epididymis showing interstitial inflammatory cell infiltrate of lymphocytes and plasma cells with pigmented macrophages. (H&E x400)

ductal lumen were present in 58%. Sperm ingestion was present in intraluminal macrophages in 62.1% and vacuolation and pigment, which are indirect evidence of sperm ingestion, were present in 86.2% and 31% respectively. Breach of epididymal ductal epithelium due to obstruction with extravasation of sperms was seen in 40% of the cases; in 75% of cases with epithelial breach and sperm extravasation, the epididymal ductal dilatation was demonstrated emphasizing the fact that epithelial breach resulted probably from increased intraductal pressure due to obstruction to sperm egress.

Changes in epididymal histology due to sperm extravasation in the interstitium was evidenced by macrophages in 11 of the 50 cases in the study group; in all these cases sperm extravasation was demonstrated. In 31 cases infiltration of the interstitium by T-lymphocytes and plasma cells was also present; inflammatory cell infiltration in the interstitium was demonstrated in all cases with epididymal ductal epithelial breach and sperm extravasation. These changes could either be the response of the interstitium due to exposure to ductal

contents or due to the local immune response to the highly antigenic sperms, especially when correlated with the ELISA results. Age did not affect inflammatory cell infiltration of the epididymal interstitium.

DISCUSSION

Under normal circumstances, spermatozoa pass from the testes to the epididymis where they travel for three days to reach the tail of the epididymis where the sperms are stored having undergone maturation during their passage through the epididymis.[20] Even though sperm output by human testes is relatively low, in the absence of ejaculation continuous production of sperms and secretions pressurizes the older sperms to be passed into the vas deferens with eventual voiding in the urine; sperm absorption by the lining cells of the epididymis also occurs.[20] In cases of obstruction to the egress of sperms, in addition to the spermatozoal degradation in the epididymis proximal to the obstruction and absorption by the lining cells of the epididymis, local regulatory mechanisms like pressure atrophy of the seminiferous tubules when the rate of sperm production exceeds sperm absorption[4] or a feedback mechanism[21] may depress spermatogenesis. Prolonged obstruction to sperm egress having an adverse effect on the spermatogenesis has been reported by various authors.[5,6,21] McConnell proposed that obstruction to distal part of excretory passage does not appear to cause permanent damage to testis, epididymis or spermatozoa but obstruction to the proximal part does so.[9] Our study does not establish the effect of obstruction on the degree of spermatogenesis; however, it shows a good correlation between grading of spermatogenesis and quantitation of mature spermatids per tubule with < 30 mature spermatids per tubule indicating some degree of hypospermatogenesis. Although the duration of the study is too short to determine the ultimate outcome of these patients, the degree of spermatogenesis may have an important bearing on the prognostication of these patients because it has been observed by Silber & Rodriguez – Rigau that there is a good correlation between quantitative analysis of testicular biopsy and the post operative sperm count.[22]

Epididymal obstruction following vasectomy has been reported to produce significant histologic changes like seminiferous tubule wall thickening and interstitial fibrosis[23,24] thickening of the basement membrane, increased phagocytosis by Sertoli cells and degeneration of spermatids[1,24] relating the changes to the increase in intraluminal pressure as the essential factor[25] with the severity of changes probably related to the duration of the obstruction[26]. These testicular histologic changes have also been attributed to the increased autoimmune activity.[23,24,27] due may be to the high prevalence of ASA of 34% to 74% and their persistence in 38% to 60% following successful reversal.[16] In experimental animals orchitis-like testicular lesions characterized by lymphocytic infiltration have been reported after vasectomy.[1] On the other hand, ASA are found in only 3% to 12% of males undergoing evaluation for infertility.[14] However, in the present study, none of the changes in testicular histology similar to those observed due to epididymal obstruction following vasectomy were seen. Nor was the possible autoimmune response to obstruction found on testicular histology as evident from the interstitium being free from any inflammatory cell infiltration. Testicular hormonal production has not been reported to be affected by obstruction to sperm flow; similar results are also reported in studies on vasectomized men.[1] These findings are corroborated by our study.

Obstruction to the egress of sperms leads to proximal distention of epididymis.[9] We found epididymal distention in 31/50 of our patients. All these patients also showed various degrees of yellowish inspissated discharge on cutting the epididymis which would represent concentrates of sperms which was also found on examination of epididymal tissue. Epididymal discharge correlated well with the grade of spermatogenesis and this difference was found to be statistically significant ($p< 0.05$).

In the examination of epididymal tissues of patients included in our study, we found that there was dilatation of epididymal ducts in 62% of the patients. This would represent effects of distal obstruction and patency of proximal epididymal ducts. In 50% of the patients, flattening of epithelium with loss of cilia was also observed probably representing effects of pressure of accumulated sperms in dilated epididymal ducts. These findings have also been reported by Phadke.[8]

Increase in pressure in the ducts would lead to breach of epididymal epithelium with resultant sperm extravasation. In our study breach in epithelium was seen in 40 % of patients with 35 % of these also showing sperm extravasation. Phadke has also reported a breach in the epithelium with extravasation of sperms in 3 / 32 cases.[8]

In our study, 58% of the patients showed the presence of macrophages in the epididymal ducts with 62% of these showing sperm phagocytosis by macrophages. These findings correlate report by Dym and Romrell that these

immunocompetent cells function to sequester sperms and their degraded fragments and prevent these antigenic materials from reaching the general circulation.[28]

Normal physiology prevents the extravasation of sperms into the interstitium, thus blocking a direct interaction between antibody producing cells and sperm proteins. In the testis this blood-testis barrier is maintained strictly by the myoid cells and Sertoli cells.[14] In the epididymis T-suppressor lymphocytes representing over 12% of the mucosal cell population in the epithelium[29] and macrophages[30,31] besides the tight epithelial junction [15] are the local immune defense. The breakdown of these barriers in the testis and epididymis results in production of ASA.[15] A breach in the epididymal epithelium would lead to a direct contact between sperm antigens and immune effector cells namely the macrophages. Thus in the present study 58% of the patients exhibited a significant ELISA in the epididymal fluid. The fact that the stimulus for antibody production was not large enough to reach the regional lymph nodes via the macrophages is evident from the fact that only 6% of the patients had significant ASA in the serum. Thus, exposure of the interstitium to the antigenic sperms when the epididymal epithelial lining is breached leads to a local cell mediated immune as postulated by Hargreave et al.[10] This response is seen as inflammatory cell infiltrate consisting of lymphocytes, macrophages and plasma cells. Macrophage infiltration has also been reported by Phadke in the interstitium who attributed them to be due to production of local autoantibodies.[8] McConnell also found focal interstitial collections of mononuclear cells with foamy pigmented cytoplasm.[9] Further, lymphocytic and plasma cell infiltrate would represent local chronic inflammatory response probably produced by foreign proteins in the interstitium in the form of sperms. In contrast to the testicular interstitial tissue which has few of lymphocytes[32], the epididymis is reported to be rich in lymphocytes.[14,29,30] The number of intraepithelial epididymal lymphocytes is reported to increase with age when the sperm degradation is significantly more in contrast to prepubertal age when the epididymal epithelium is relatively free of lymphocytes.[29] However, interstitial lymphocytic and plasma cell infiltration is indicative of a local immune response. Thus, 62% patients in the present study showed a local inflammatory infiltrate in the interstitium and in all these cases epididymal ductal epithelial breach and sperm extravasation was demonstrated. Additionally, 100% of the cases in whom epididymal fluid could be obtained had significant ELISA further strengthening the probability of a local cell-mediated immune response in part being responsible for the histologic changes seen in the patients under review.

The role of local immune reaction in obstructive infertility has not been widely studied. The present study has put across strong evidence to support the hypothesis that postulates that obstructive azoospermia causes breach in the epididymal epithelium due to increased intraluminal pressure. While the exposure to the antigenic sperms may not be sufficient to produce a strong humoral response with detectable levels of circulating antisperm antibodies, repeated exposure to small amounts of extravasated sperms in the epididymal interstitium would be sufficient to produce a cell mediated immune response locally with its attendant, some irreversible, effects on the epididymis and sperms. Since epididymis is the primary site of sperm maturation, irreversible changes in its structure are likely to affect the morphology and maturation of sperms. It is possible that dysfunction of epididymal sperm storage can be a cause of infertility.[33] Our study also overcomes the one clear adverse effect of ICSI. ICSI has spread the idea amongst clinicians that it is so effective that investigation for patient or even a definition of the cause of his infertility is no longer necessary or economically viable.[34] Indeed there is widespread view that as long as a few sperms can be identified for use in an ICSI procedure, no clinical evaluation apart from routine semen analysis is necessary. However, in patients of obstructive azoospermia, the pregnancy rate with ICSI using sperms aspirated from the epididymis in terms of pregnancies per cycle has been reported to be 41% - 47%.[35,36] It has been shown that in 49% of failed cycles of ICSI, fertilization failure was related to a sperm factor like the absence of motile spermatozoa for injection, or the injection of morphologically abnormal spermatozoa.[37]

Thus, the study of function and morphology of spermatozoa in patients of male infertility becomes imperative not only to explain the persistence of infertility after surgical removal of cause but also to explain failure of assisted reproduction. The findings of the present study, therefore, go a long way to reiterate the importance of the application of basic sciences in the study of the pathophysiological changes resulting in and from primary obstructive infertility in males.

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