Mannose-Binding Lectin Deficiency Facilitates Abdominal Candida Infections in Patients with Secondary Peritonitis

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Mannose-binding lectin (MBL) deficiency due to variations in the MBL gene is associated with increased susceptibility to infections. In this study, the association between MBL deficiency and the occurrence of abdominal yeast infection (AYI) in peritonitis patients was examined. Eighty-eight patients with secondary peritonitis requiring emergency laparotomy were included. MBL genotype (wild type [WT] versus patients with variant genotypes), MBL plasma concentrations, and Candida risk factors were examined in patients with and those without AYI (positive abdominal yeast cultures during [re]laparotomy). A variant MBL genotype was found in 53% of patients with AYI and 38% of those without AYI (P = 0.18). A significantly higher proportion of variant patients had an AYI during early peritonitis (during first laparotomy) than WT patients (39% versus 16%, respectively; P = 0.012). Patients with AYI had lower MBL levels than did patients without AYI (0.16 μg/ml [0.0 to 0.65 μg/ml] versus 0.65 μg/ml [0.19 to 1.95 μg/ml]; P = 0.007). Intensity of colonization (odds ratio [OR], 1.1; 95% confidence interval [CI], 1.0 to 1.1), MBL plasma concentrations of <0.5 μg/ml (OR, 4.5; 95% CI, 1.2 to 16.3), and numbers of relaparotomies (OR, 1.7; 95% CI, 1.0 to 2.8) were independently associated with AYI. In summary, deficient MBL plasma levels were independently associated with the development of AYI in patients with secondary peritonitis and seemed to facilitate early infection.

Secondary peritonitis is a clinical condition frequently observed in surgical wards and intensive care units (ICUs) (15). In spite of major advances in (intensive) care and antimicrobial therapy, mortality in peritonitis has remained approximately 25% for decennia (25, 34). Morbidity in patients with peritonitis also tends to be extensive, with long hospital and ICU stays and long periods of mechanical ventilation (25). Especially when peritonitis persists or recurs, notwithstanding optimal management, and tertiary peritonitis develops, mortality increases to >50% (29). When Candida species are recovered from abdominal isolates from cases of peritonitis, mortality is 60 to 70% when untreated (32). Up to 40% of peritonitis patients have positive abdominal yeast cultures (10, 12, 38), and depending on the body site, Candida species are among the most commonly cultured microorganisms in surgical infections (39). In a recent study, the intraoperative detection of yeast was one of the few independent risk factors for mortality and increased morbidity in cases of secondary peritonitis (38). Yeast is the fourth leading cause of all nosocomial bloodstream infections in the United States, taking third place in bloodstream infections in ICUs (46). Moreover, the incidence of fungal infections with a vast majority of Candida species is increasing (19), increasing numbers of strains of which are becoming resistant to antifungal agents (15, 22).

Recently, the complement protein mannose-binding lectin (MBL) has been shown to play a role in the first line of defense against Candida albicans (20, 26). MBL binds to a wide variety of microorganisms through a carbohydrate recognition domain, exhibiting strong binding to Candida and other yeast species (21, 26, 33). The complement system is activated via this lectin pathway, causing opsonization and direct lysis of microorganisms (21).

Deficiency of MBL is due to variations in the MBL gene, which are present in 20 to 40% of the population. These polymorphisms have been associated with increased susceptibility to a multitude of clinical infections in various conditions (14) such as infectious complications following surgery (40, 47) but also fungal infections, i.e., recurrent vulvovaginal candidiasis and necrotizing pulmonary aspergillosis (2, 7).

The increased burden of infection caused by MBL deficiency seems to weigh particularly on patients with primary or secondary depression of immune systems (14). For instance, critically ill patients with genetically variant MBL alleles or low serum levels have an increased risk of developing and succumbing to sepsis (16, 17). Peritonitis patients are often critically ill and usually require intensive care treatment. In the present study, the role of MBL plasma levels (phenotype) and genetic variants of MBL (genotype) in the development of abdominal yeast infection (AYI) in patients with secondary peritonitis, at index laparotomy, and during the course of disease is examined.
MATERIALS AND METHODS

Patients and controls. In this prospective cohort study, patients with peritonitis caused by the perforation or infection of a visceral organ, by necrosis of part of the gastrointestinal (GI) tract, or by postoperative peritoneal infection were included. Exclusion criteria were patients aged <18 and >80 years and patients with acute pancreatitis. Patients were included when they underwent emergency laparotomy, referred to as the “index laparotomy,” in which peritonitis was confirmed macroscopically and microbiologically. Operative management of peritonitis was comprised of elimination of the infectious focus and abdominal lavage with saline (0.9%). Relaparotomy was performed in a planned setting or on demand (indicated by clinical deterioration or failure to improve).

Controls for genotyping and plasma MBL concentrations were recruited from a population of healthy blood bank donors (n = 97). The study was approved by the medical ethical committee, and written informed consent was obtained from all patients or their legal representatives when appropriate.

Definitions. AYI was defined as a positive yeast culture from abdominal fluid sampled during (re)laparotomy with subsequent features of infection/systemic inflammatory response syndrome (see below). Yeast sepsis was defined as a positive culture from a sterile site that could not have been contaminated directly, such as blood or noncontiguous organs. Yeast colonization was defined as one or more positive yeast cultures from sputum, rectum, urine, or wound surface. Intensity of colonization was calculated by dividing the total number of positive yeast cultures by the total number of cultures performed (excluding blood cultures), as described previously by Pittet et al. (36).

Systemic inflammatory response syndrome was defined as severe sepsis, and septic shock (developing within 24 h of enrollment in the study) were defined in accordance with the recommendations of the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference (4). Risk factors associated with Candida infection (36), Candida peritonitis (10, 11), and candidemia (3) in multivariate analysis, as mentioned in recent literature, were surveyed.

Sampling and measurements. During surgery, cultures of abdominal fluid as well as blood were performed using a collection system for aerobic and anaerobic organisms (Bact/Alert; Biomérieux, Durham, NC). Postoperative cultures were performed routinely and at the discretion of the physician in charge of the patient. Standard empirical antibiotic treatment for severe peritonitis, received by all patients, consisted of a combination of amoxicillin, gentamicin, and metronidazole. This regimen was adjusted according to culture results. When yeast was cultured, fluconazole was the first antifungal agent of choice. All patients received selective bowel decontamination drugs orally as described previously by De Jonge et al. (0.5 g of an oral paste containing 2% polymyxin E, 2% tobramycin, and 2% amphotericin B) and 100 mg polymyxin E, 80 mg tobramycin, and 500 mg amphotericin B administered through gastric tubes four times daily (9).

Blood was sampled during or directly following surgery. MBL concentrations were measured in citrated (0.109 M) plasma. DNA was extracted from the cell pellet.

MBL was measured in an enzyme-linked immunosorbent assay as described previously by Tack et al. (41). The detection limit was 0.02 μg/ml. Nucleic acids were isolated according to a solid-phase extraction method (Boom method) as previously described (5).

The genetic variants associated with deficient MBL production are nucleotide polymorphisms situated in the exon 1 region of the structural gene on codons 52, 54, and 57 (variants D, B, and C, respectively) and in the promoter region flanking exon 1 at positions +4, +70, –336, –349, and –427 and the deletion of nucleotides –329 to –324. According to the positions of nucleotide substitutions, these promoter polymorphisms are called H/L, X/Y, and P/Q variants (28). Exon 1 wild-type individuals (WT) are referred to as AA, heterozygous individuals are referred to as AO, and homozygous or compound individuals are referred to as OO. The L and the X promoter gene variants also display very low (H/L1) and high (H/L2) expression levels of MBL production (23). In this study, WT patients are compared with OO patients referred to as OO. The L and the X promoter gene variants also display very low (H/L1) and high (H/L2) expression levels of MBL production (23, 27, 28). Exon 1 AA patients and controls provided significantly higher levels of MBL (Table 1) than did AO PCR products. Exon 1 alleles were determined by a modified sequence reaction method (25, 27). The sense primer 5′-GTCTAGGCAGATTGATGAC-3′ and reverse primer 5′-GTCATGCTGTTGCAAGGAAACCTTGATCTACTGGA-3′ were used for the MBL promoter region (forward primer 5′-TATGACCTCTTGCAAGGCGCAACGT-3′ and reverse primer 5′-GTCTAGCCAGATTGATGAC-3′) and exon 1 (forward primer 5′-GTCTAGGCAGATTGATGAC-3′ and reverse primer 5′-CTTCCAGAGGAANCTGCTGGGAT-3′).

Sequence reactions. The genomic PCR products were sequenced in both orientations after amplification with the Qiagen PCR purification kit (QIAGEN GmbH, Hilden, Germany). Five microliters of purified PCR product was used as a template together with the sense or the antisense primer (250 nM) used to obtain this PCR product. Four microliters of reaction mixture from the Big Dye Terminator cycle sequencing ready reaction kit version 1.1 (PE Applied Biosystems, Warrington, United Kingdom) was mixed with 2 μl of Big Dye Terminator dilution buffer in a total volume of 20 μl. Cycle conditions were 10 at 95°C and 4 min at 60°C for 50 cycles in a 96-well polycarbonate plate in an Omnigene thermocycler (Hybaid, Teddington, Middlesex, United Kingdom) with simulated tube control and calibration factor 200. The sequencing samples were purified in Multiscreen plates (Millipore, Molsheim, France) and were subsequently loaded onto an ABI 377XL automated DNA sequencer (PE Applied Biosystems).

Statistical analysis. Known yeast risk factors and MBL genotype and phenotypes were compared in peritonitis patients with AYI, initially or during the course of disease, were compared to those of peritonitis patients without AYI. Furthermore, the proportion of patients with a positive culture at index laparotomy or at relaparotomy (during the course of disease) was determined in relation to genotype. Results are presented as medians with interquartile ranges (IQRs) or as quantiles with percentages. The nonparametric Mann-Whitney U test was used to evaluate statistical differences between two independent groups of data. Fisher’s exact test was used to compare proportions between groups. Univariate and multivariate analyses were performed by means of binary logistic regression. Factors associated with AYI (P < 0.15) were then entered in a multivariate model unless predictive factors were strongly correlated with each other, and only one factor with the strongest association (based on the one-variable-model chi-square test) was then chosen. With respect to the MBL level cutoffs, the two cutoffs most commonly used in the literature (13, 43) were tested as described above. All P values were two sided, with P values of less than 0.05 considered to indicate statistical significance. Statistical analysis was performed using SPSS (Chicago, IL) 12.0.1.

RESULTS

Patients. Eighty-eight consecutive peritonitis patients were included in this study. The etiology of peritonitis was perforation in 39 patients (44%), necrosis in 16 patients (18%), and anastomotic leakage in 28 patients (32%). Peritonitis originated from either the upper (stomach, duodenum, and jejunum) or lower (ileum, colon, sigmoid, and rectum) GI tract in 14 and 74 patients, respectively. All patients had polymicrobial peritonitis with or without yeast. The antibiotic treatment was started empirically (cefuroxime [or amoxicillin], gentamicin, and metronidazole) in all patients. Antibiotic regimens were adapted if necessary after culture results became known.

Short-term mortality (n = 11 [13%]) was all due to septic complications. With regard to long-term mortality (n = 24 [27%]), 18 patients died from the results of sepsis, 4 died due to malignancy, and 2 died due to cardiovascular complications. A total of 223 laparotomies were performed in 88 patients, 55 of which were performed prior to the index laparotomy, 88 of which were index laparotomies, and 80 of which were relaparotomies (32 planned and 18 on demand).

Frequencies of exon 1 variants in the peritonitis group were comparable to frequencies in the regional population (Table 1). All four exon 1 variant alleles (A, B, C, and D) were encountered at a frequency comparable to that of the control group and the general European population as described in the literature (23, 27, 28). Exon 1 AA patients and controls produced significantly higher levels of MBL (Table 1) than did AO patients and controls produced significantly higher levels of MBL (Table 1) than did AO patients and controls produced significantly higher levels of MBL (Table 1) than did AO patients and controls produced significantly higher levels of MBL (Table 1) than did AO patients and controls produced significantly higher levels of MBL (Table 1) than did AO patients and controls produced significantly higher levels of MBL (Table 1) than did AO
TABLE 1. Structural exon 1 MBL genotypes and plasma concentrations of patients with secondary peritonitis and healthy controls

| Genotype | Peritonitis patients (n = 88) | Controls (n = 97) |
|----------|-----------------------------|------------------|
|          | No. (%)                     | MBL level (µg/ml) (IQR) | No. (%)                     | MBL level (µg/ml) (IQR)* |
| AA       | 53 (60)                     | 1.2 (0.6–2.3)      | 52 (54)                     | 2.2 (1.3–3.1)*          |
| AO       | 30 (34)                     | 0.1 (0.0–0.3)      | 41 (42)                     | 0.4 (0.0–0.5)           |
| OO       | 5 (6)                       | 0.0 (0.0–0.0)      | 4 (4)                       | 0.0 (0.0–0.1)           |

* P value was 0.005 in comparison to patients.

<sup>a</sup>, the P value was 0.005 in comparison to patients.

<sup>b</sup> P value for the comparison between those with AYI and those without AYI.

<sup>c</sup> Variant MBL genotypes are AO/OO and LXA/LXA.

<sup>d</sup> 48 h AB, more than 48 h of antibiotic treatment before positive yeast culture; TPN, total parenteral nutrition; AYI, patients with AYI; AYI, patients without AYI.

<sup>e</sup> P value for the comparison between those with AYI and those without AYI.

MBL and abdominal yeast infection

MBL and abdominal yeast infection, which are known to be associated with various levels of MBL, were similar to previously reported values (23). Three LXA/LXA patients who produced low MBL levels (0.08, 0.12, and 0.22 µg/ml) were encountered. For analysis, 50 WT (AA) (n = 50) patients were compared with 38 variant (AO/OO [n = 35] and LXA/LXA [n = 3]) peritonitis patients.

Yeast. AYI was observed in 28 (32%) patients (Table 2). Twenty of these 28 patients (71%) were also colonized with yeast, compared to 30 of the 60 patients without AYI (P = 0.062). Fifty-seven percent (n = 50) of all patients were colonized with yeast during their hospital stays. A total of 1,620 cultures (excluding blood cultures) were obtained. In patients with AYI, a median of 13 (range, 5 to 26) cultures were performed, and in non-AYI patients, seven (range, 2 to 23) cul-

| TABLE 2. Risk factors for Candida infection, peritonitis, and bloodstream infections in the total group of peritonitis patients, patients with AYI, and patients without AYI |

| Parameter | Value for group | P value<sup>b</sup> |
|-----------|-----------------|---------------------|
| Patient characteristic | Total (n = 88) | AYI (n = 28) | AYI (n = 60) |
| Age (yr) (IQR) | 62 (43–74) | 62 (40–72) | 62 (48–78) | 0.30 |
| No. (%) of patients with: Yeast colonization | 50 (57) | 20 (71) | 30 (50) | 0.0062 |
| Candidemia | 5 (6) | 4 (14) | 1 (2) | 0.046 |
| Sepsis | 74 (84) | 22 (79) | 52 (87) | 0.34 |
| Severe sepsis | 58 (66) | 16 (57) | 42 (70) | 0.24 |
| Septic shock | 12 (14) | 2 (7) | 10 (16) | 0.24 |
| 28 days mortality | 11 (13) | 4 (14) | 7 (12) | 0.73 |
| 180 days mortality | 25 (26) | 10 (36) | 15 (25) | 0.30 |
| No. of days (IQR) of: ICU stay | 7 (2–17) | 6 (2–22) | 8 (1–15) | 0.68 |
| Ventilation | 5 (1–14) | 6 (1–11) | 5 (1–14) | 0.97 |
| Hospital stay | 29 (17–56) | 30 (19–66) | 28 (16–53) | 0.96 |
| Risk factors | | | |
| % Colonization intensity (IQR) | 17 (0–33) | 36 (22–57) | 0 (0–21) | <0.001 |
| APACHE-II score (IQR) | 15 (12–18) | 16 (12–18) | 15 (12–19) | 0.66 |
| No. (%) of patients with: APACHE-II score >17 | 37 (42) | 11 (39) | 26 (43) | 0.72 |
| Respiratory failure | 18 (21) | 5 (18) | 13 (22) | 0.68 |
| Cardiovascular failure | 27 (31) | 7 (25) | 20 (33) | 0.43 |
| Upper GI tract infection | 14 (16) | 8 (29) | 6 (10) | 0.033 |
| >48 h AB | 19 (22) | 7 (25) | 12 (20) | 0.60 |
| Female gender | 44 (50) | 12 (43) | 32 (53) | 0.36 |
| Renal failure/hemodialysis | 19 (22) | 4 (14) | 15 (25) | 0.26 |
| TPN | 46 (52) | 18 (64) | 28 (47) | 0.13 |
| Central venous catheter | 56 (64) | 19 (69) | 37 (62) | 0.57 |
| No. of abdominal operations (IQR) | | | |
| Prior to index | 1 (0–1) | 1 (0–1) | 1 (0–1) | 0.86 |
| Relaparotomies | 1 (0–1) | 1 (1–2) | 0 (0–1) | 0.025 |
| MBL | | | |
| No. (%) of patients with variant MBL genotype | 38 (43) | 15 (54) | 23 (38) | 0.18 |
| MBL plasma concn (µg/ml) (IQR) | 0.41 (0.10–1.40) | 0.16 (0.0–0.65) | 0.65 (0.19–1.95) | 0.007 |
| No. (%) of patients with MBL level of: <0.25 µg/ml | 34 (39) | 16 (57) | 18 (30) | 0.026 |
| <0.50 µg/ml | 45 (51) | 20 (71) | 25 (42) | 0.019 |
MBL levels in patients with yeast colonization were not different between those with and without AYI and between those with and without AYI (AYI+) and AYI (AYI−) (Fig. 2 and Table 2) and controls (median 0.95 µg/ml [IQR, 0.05 to 2.35 µg/ml]; P = 0.002) (Fig. 2).

Low-MBL-producing patients, identified by cutoff levels of 0.25 or 0.5 µg/ml, had significantly more AYIs. At a cutoff level of 0.25 µg/ml, 16 of 34 (47%) low producers versus 12 of 54 (22%) high producers had AYI (P = 0.026); at a cutoff level of 0.5 µg/ml, 20 of 45 (44%) low producers versus 8 of 43 (19%) high producers had AYI (P = 0.019).

Multivariate analysis. An MBL cutoff value of <0.25 µg/ml was a weaker predictor than a cutoff value of <0.50 µg/ml (one-variable-model chi-square value of 5.072 versus 5.881, respectively) and, hence, was not entered into the multivariate model. The factors that were independently associated with the development of AYI were intensity of colonization (odds ratio [OR], 1.08; 95% confidence interval [CI], 1.04 to 1.11 per percentage of increase; P < 0.001), MBL plasma concentrations of <0.5 µg/ml (OR, 4.47; 95% CI, 1.22 to 16.28; P = 0.023), and number of relaparotomies (OR, 1.70; 95% CI, 1.03 to 2.81 per relaparotomy; P = 0.038).

**DISCUSSION**

Peritonitis patients who encountered an AYI had lower plasma MBL levels than did patients who did not develop AYI. The plasma MBL level was measured in blood sampled during or shortly after emergency surgery. MBL levels start to rise only about 5 days after the initiation of an inflammatory response (43), so MBL levels in the current study were likely to approximate baseline levels and were probably not yet influenced by the abdominal infection and/or operation. MBL plasma levels below 0.5 µg/ml were independently associated with the development of AYIs, as were intensity of colonization and the number of relaparotomies. Increased intensity of colonization may lead to an increased burden of the fungal microbial load and thus an increased incidence of infection. The importance of colonization is illustrated by the fact that...

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**FIG. 1.** Proportional differences of early (during index laparotomy), late (during relaparotomy), or no AYI in patients with WT or variant MBL genotypes. *P* value of the comparison of proportions of patients with no, early, or late AYI between WT and variant groups in a chi-square test.

**FIG. 2.** Scatter plots of MBL plasma concentrations in patients with and those without AYI (AYI+ and AYI−, respectively) and controls (median of 0.95 µg/ml [IQR, 0.05 to 2.35 µg/ml]; P = 0.002) (Fig. 2).
Candida colonization or infection with an identical strain frequently preceded (bloodstream) infection in nonneutropenic patients (44, 45). The extent (intensity) of Candida colonization was shown to be an independent factor for Candida infection (30, 36). Furthermore, positive peritoneal yeast cultures were associated with mortality in peritonitis patients (11, 31). The number of relaparotomies is likely a reflection of disease severity and protracted abdominal infection with an increased risk of AYI.

Patients with MBL levels of <0.5 μg/ml had a risk of developing AYI that was 4.5 times greater than that for patients with higher MBL plasma levels. The pathophysiology of the relation between MBL deficiency and the early appearance of yeast cultured from the abdominal fluid is possibly the reduced clearance capacity of the complement system of abdominal yeast in individuals with an impaired MBL pathway. WT patients may be able to clear yeast more efficiently, postponing the development of a yeast infection to a state of generally depressed immunity later in the disease. Peritonitis patients may develop immunosuppression as a result of initially up-regulated responses during intra-abdominal infection combined with the effects of surgery. Surgery itself can suppress the immune response (42), as was confirmed in experimental studies reported previously (1, 37). Conditional immunosuppression plus low functional MBL levels may reduce the inhibition of yeast proliferation. In the current study, MBL plasma levels were lower in peritonitis patients with the WT structural genotype (AA) than in AA controls, which may indicate MBL consumption.

Patients with variant MBL genes also have significantly lower peritoneal MBL levels than do WT AA patients (24), but in both WT and variant patients, these levels are very low compared to plasma levels. MBL-deficient patients may thus have relatively less biologically functional MBL available in plasma as well as in the abdomen to counteract yeast proliferation. These patients may benefit from early MBL suppletion therapy, which was previously shown to reduce mortality in experimental candidemia (26).

The 0.5-μg/ml and not the 0.25-μg/ml MBL level cutoff was independently related with AYI in two separate models. This cutoff point has also been associated with other clinical conditions. An association between adverse outcome in ICU patients and severe MBL deficiency using the 0.5-μg/ml cutoff was found (18). There was an increased susceptibility to infections in chemotherapy patients with MBL levels of 0.5 μg/ml or less (35). Also, sepsis patients with baseline MBL deficiencies failed to produce MBL at levels greater than 0.5 μg/ml (8).

The baseline cutoff level of <0.5 μg/ml in plasma reliably identifies individuals with variant exon 1 alleles (sensitivity of 100% and specificity of 83%) (43). However, the genotype of the patient does not ultimately reflect MBL production. Not all AO individuals are deficient, while some AA individuals with normal promoter haplotypes are indeed deficient, as was observed in British Caucasians (6). Thus, MBL deficiency can be adequately detected by measuring plasma levels by a simple enzyme-linked immunosorbent assay.

Abdominal yeast infections were encountered with an incidence comparable to those reported in previous studies of secondary peritonitis (10, 12, 38). A significantly higher proportion of MBL variant patients had an early AYI (at index laparotomy) than WT patients. Thus, MBL genetic variation may amount for the early emergence of AYI.

The diagnosis and treatment of these yeast infections are challenging and largely empirical. Candida is a part of the normal commensal flora, so the interpretation of a positive yeast culture can be difficult. Furthermore, the classical patient that develops a yeast infection is incapable of mounting a normal host response and thus does not stereotypically present clinical signs of infection. Sedation and mechanical ventilation while in the ICU may also hamper clinical assessment and early diagnosis, which are vital to proper and rapid treatment. Diagnosis is frequently delayed because culture results take a few days to become interpretable as being positive or negative. MBL levels are a promising tool to recognize patients with a high risk of fungal infection. A future risk prediction score may be based upon the present prediction model with colonization intensity, baseline MBL level (at a cutoff of <0.5 μg/ml), and number of relaparotomies as predictive variables. Antifungal treatment may be targeted more appropriately.

In summary, the incidence of abdominal yeast infection is high in secondary peritonitis (32%). MBL plasma levels of <0.5 μg/ml, intensity of colonization, and the number of relaparotomies are independently associated with the development of AYIs in patients with secondary peritonitis. A variant MBL genotype may facilitate the early emergence of AYI during peritonitis.

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