
بسم الله الرحمن الرحيم

NON AMYLOID FIBIRILLAR GLOMERULUPATHIES

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IN ZUMS

- **INTRODUCTION**

GLOMERULAR DISEASE MAY BE ASSOCIATED WITH THE APPEARANCE OF **FIBRILLAR DEPOSITS IN THE MESANGIUM OR GLOMERULAR BASEMENT MEMBRANE.** THE FIBRILS ARE CONGO RED POSITIVE IN **AMYLOIDOSIS** AND ARE TYPICALLY **CONGO RED NEGATIVE** IN OTHER FORMS. THE MOST COMMON FORMS OF NONAMYLOID FIBRILLARY GLOMERULAR DEPOSITION DISEASES ARE **FIBRILLARY GLOMERULONEPHRITIS** AND **IMMUNOTACTOID GLOMERULOPATHY**.

- FIBRILLARY GLOMERULONEPHRITIS AND IMMUNOTACTOID GLOMERULOPATHY ARE **UNCOMMON**, BUT DISTINCTLY DIFFERENT, CAUSES OF GLOMERULAR DISEASE. BOTH DISORDERS RESULT FROM **DEPOSITS DERIVED FROM IMMUNOGLOBULINS**.

OTHER FORMS OF NONAMYLOID FIBRILLARY DEPOSITION DISEASE HAVE BEEN DESCRIBED IN WHICH THE DEPOSITS ARE COMPOSED OF FIBRONECTIN (**FIBRONECTIN** GLOMERULOPATHY) OR ATYPICAL TYPE III COLLAGEN FIBRILS (**COLLAGENOFIBROTIC** GLOMERULOPATHY).

- **FIBRILLARY AND IMMUNOTACTOID DISEASES**

FIBRILLARY GLOMERULONEPHRITIS AND IMMUNOTACTOID GLOMERULOPATHY ARE **UNCOMMON** DISORDERS, BEING PRESENT IN **0.5 TO 1.4** PERCENT OF NATIVE KIDNEY BIOPSIES. THEY ARE SEPARATE DISORDERS, WITH **FIBRILLARY** GLOMERULONEPHRITIS ACCOUNTING FOR APPROXIMATELY **85 TO 90** PERCENT OF CASES.

THE IDENTIFICATION OF THE PROTEIN DNAJ HEAT SHOCK PROTEIN FAMILY (HSP40) MEMBER B9 (**DNAJB9**) IN THE GLOMERULI OF PATIENTS WITH FIBRILLARY GLOMERULONEPHRITIS BUT NOT IN THOSE WITH IMMUNOTACTOID GLOMERULOPATHY HAS MADE IT CLEAR THAT THE **TWO ARE DISTINCT, PATHOGENICALLY UNRELATED** DISEASE ENTITIES.

- **PATHOLOGY**

THE DIAGNOSIS OF **FIBRILLARY** GLOMERULONEPHRITIS IS ESTABLISHED BY KIDNEY BIOPSY, WITH THE PATHOGNOMONIC CHANGES SEEN ON **ELECTRON MICROSCOPY** AND WITH **IMMUNOFLUORESCENCE** OR **IMMUNOHISTOCHEMICAL STAINING FOR DNAJB9.**

- **LIGHT MICROSCOPY**

THE LIGHT MICROSCOPIC FINDINGS ARE **NONDIAGNOSTIC AND VARIABLE,** SHOWING PATTERNS THAT MAY BE SEEN WITH OTHER GLOMERULONEPHRITIDES. THESE INCLUDE **FOCAL MESANGIAL** (THE **MOST COMMON**) OR **DIFFUSE PROLIFERATIVE** OR **MEMBRANOPROLIFERATIVE** GLOMERULONEPHRITIS (WITH OR WITHOUT CRESCENT FORMATION), A **MEMBRANOUS** PATTERN, **AND MESANGIAL EXPANSION WITH AMORPHOUS MATERIAL** THAT MAY BE SUGGESTIVE OF AMYLOIDOSIS OR LIGHT CHAIN DEPOSITION DISEASE . A **CRESCENTIC GLOMERULONEPHRITIS CAN BE SEEN IN 17 TO 50** PERCENT OF CASES, BUT CASES WITH >50 PERCENT OF GLOMERULI INVOLVEMENT ARE RARE.

- **IMMUNOFLUORESCENCE**

IMMUNOFLUORESCENCE MICROSCOPY IS POSITIVE FOR IMMUNOGLOBULIN G **(IGG), C3, AND BOTH KAPPA AND LAMBDA** (IE, **POLYCLONAL**) LIGHT CHAINS. THERE IS USUALLY PREDOMINANT DEPOSITION OF SOME IGG SUBCLASSES, PARTICULARLY **IGG4** AND TO A LESSER EXTENT **IGG1**. IMMUNOGLOBULIN A (IGA), IMMUNOGLOBULIN M (IGM), AND C1Q DEPOSITION MAY ALSO BE SEEN.

THE FIBRILLARY DEPOSITS MAY BE SO EXTENSIVE THAT THE IGG DEPOSITION MAY BE LINEAR, SIMILAR TO THAT SEEN IN ANTI-GLOMERULAR BASEMENT MEMBRANE ANTIBODY DISEASE .EXTRAGLOMERULAR STAINING, MOST COMMONLY INVOLVING THE **TUBULAR BASEMENT MEMBRANES**, HAS BEEN REPORTED IN **30 TO 50** PERCENT OF CASES. RARE CASES OF IMMUNOGLOBULIN-NEGATIVE FIBRILLARY GLOMERULONEPHRITIS HAVE ALSO BEEN DESCRIBED. THE DETECTION OF MONOTYPIC DEPOSITS BY STANDARD FROZEN SECTION IMMUNOFLUORESCENCE SHOULD BE CONFIRMED BY PARAFFIN IMMUNOFLUORESCENCE, WHICH MAY REVEAL "MASKED" POLYTYPIC DEPOSITS IN NEARLY ONE-HALF OF CASES AND THEREBY PREVENT THE MISDIAGNOSIS OF THESE PATIENTS WITH MONOCLONAL FIBRILLARY GLOMERULONEPHRITIS. IMMUNOFLUORESCENCE STAINING FOR IMMUNOGLOBULIN HEAVY CHAIN/LIGHT CHAIN ON KIDNEY BIOPSIES CAN ALSO BE USED TO CONFIRM OR EXCLUDE MONOCLONALITY IN THESE CASES.

- •**ELECTRON MICROSCOPY**

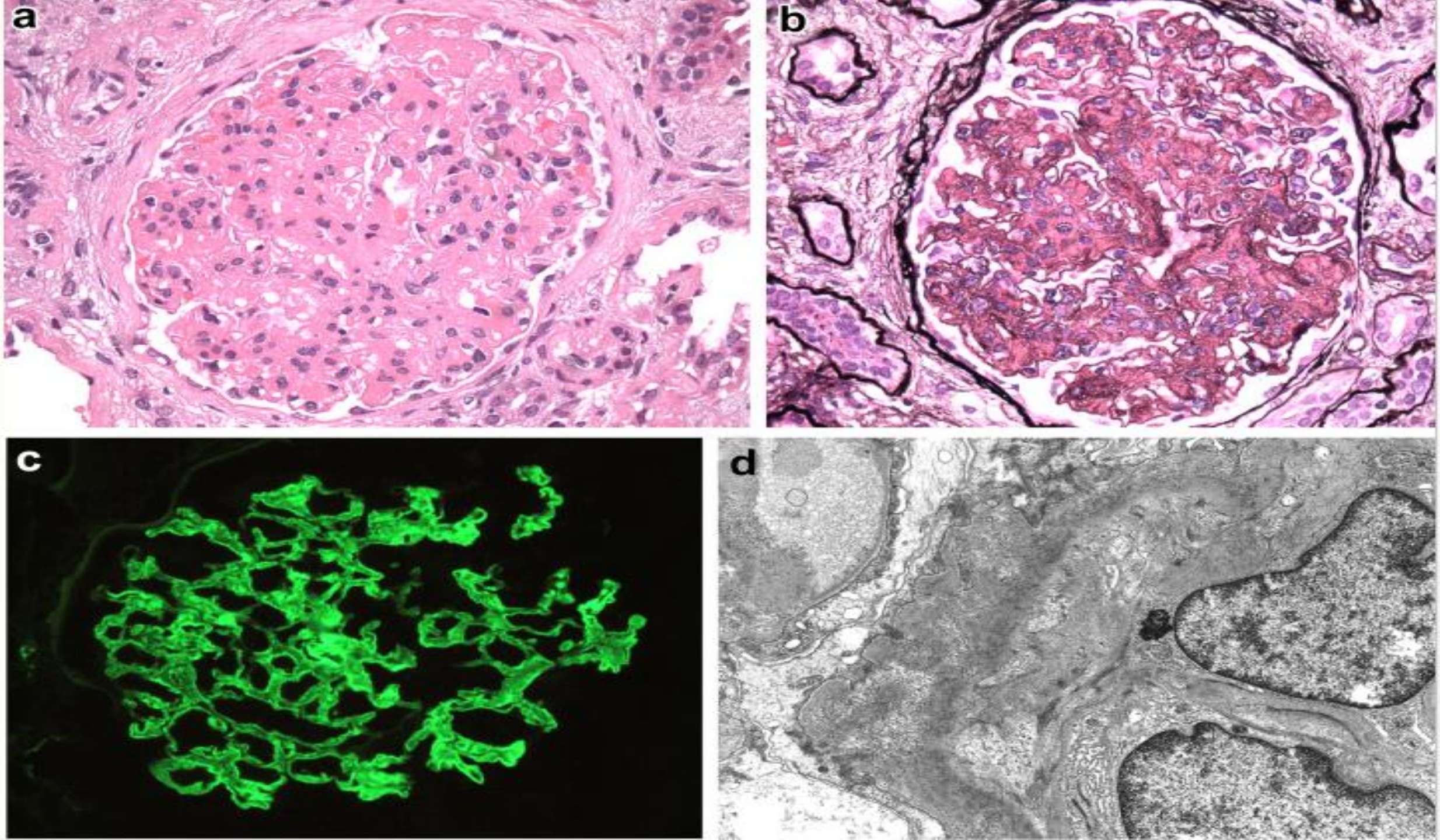
ELECTRON MICROSCOPY SHOWS RANDOM FIBRILLAR DEPOSITS IN THE MESANGIUM AND GLOMERULAR CAPILLARY WALLS THAT ARE CLEARLY DISTINCT FROM THOSE SEEN IN AMYLOIDOSIS. THE FIBRILS ARE **LARGER THAN THOSE IN AMYLOIDOSIS** (**16 TO 24 NM IN FIBRILLARY** GLOMERULONEPHRITIS VERSUS **10 NM IN DIAMETER IN AMYLOIDOSIS**).

THE FIBRILS IN **FIBRILLARY** GLOMERULONEPHRITIS ARE **RANDOMLY** ARRANGED, WHEREAS **MICROTUBULES OBSERVED IN IMMUNOTACTOID** GLOMERULOPATHY FORM **PARALLEL BUNDLES**.

•**CONGO RED STAINING**

IN CONTRAST TO AMYLOID FIBRILS, THE FIBRILS IN FIBRILLARY GLOMERULONEPHRITIS **USUALLY DO NOT STAIN WITH CONGO RED OR THIOFLAVINE-T OR WITH ANTIBODIES TO A SPECIFIC LIGHT CHAIN (EITHER LAMBDA OR KAPPA) OR TO SERUM AMYLOID A**.

HOWEVER, **ONE STUDY DESCRIBED A SERIES OF PATIENTS WITH FIBRILLARY GLOMERULONEPHRITIS WHOSE GLOMERULAR DEPOSITS WERE CONGO RED POSITIVE** . GIVEN THESE FINDINGS, **THE PRESENCE OR ABSENCE OF CONGO RED STAINING SHOULD NOT SOLELY BE USED TO DISTINGUISH BETWEEN FIBRILLARY GLOMERULONEPHRITIS AND RENAL AMYLOIDOSIS.** OTHER DIAGNOSTIC METHODS, SUCH AS **MASS SPECTROMETRY AND IMMUNOHISTOCHEMISTRY (FOR DNAJB9),** ARE IMPORTANT IN MAKING THIS DISTINCTION..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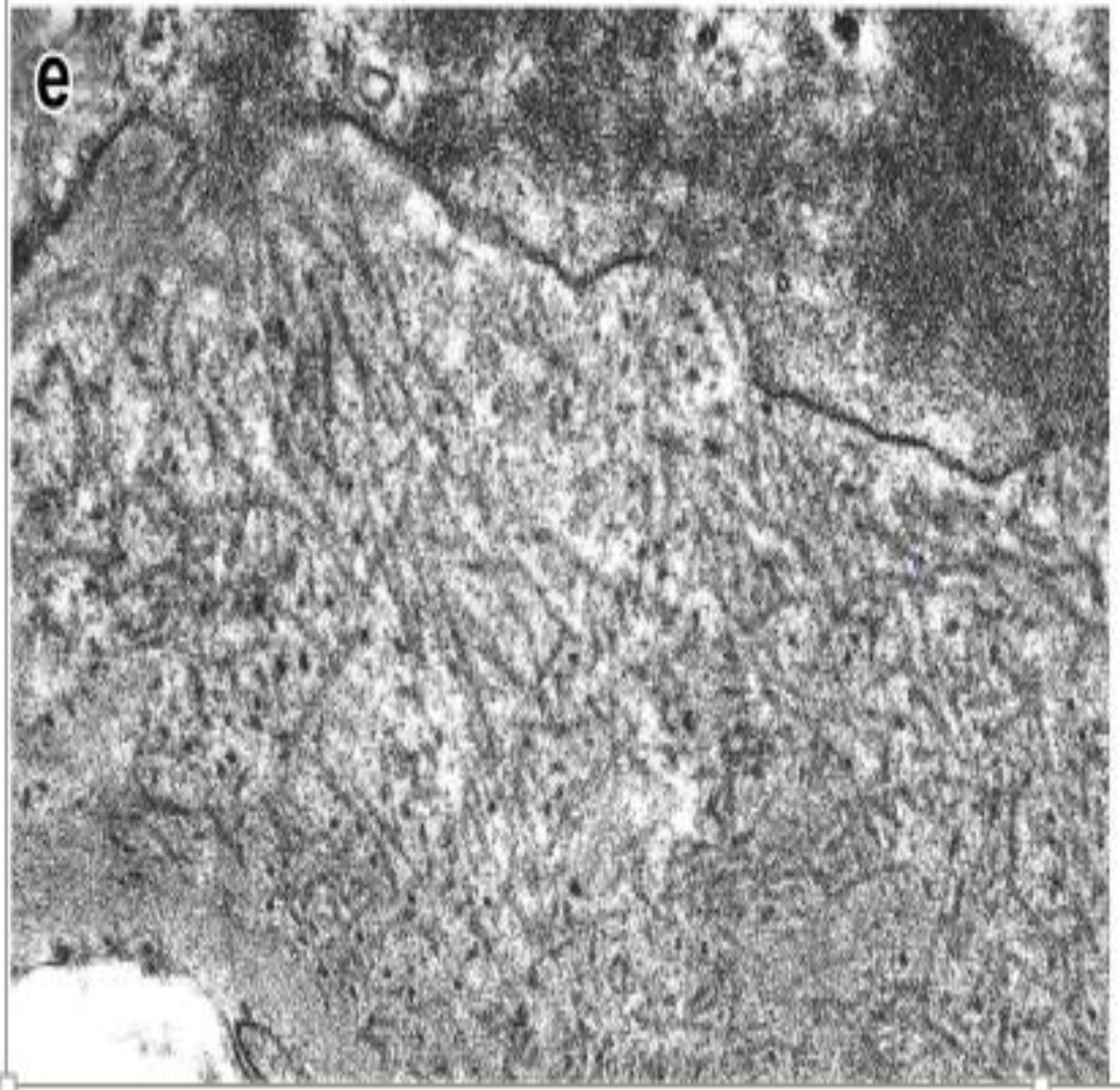
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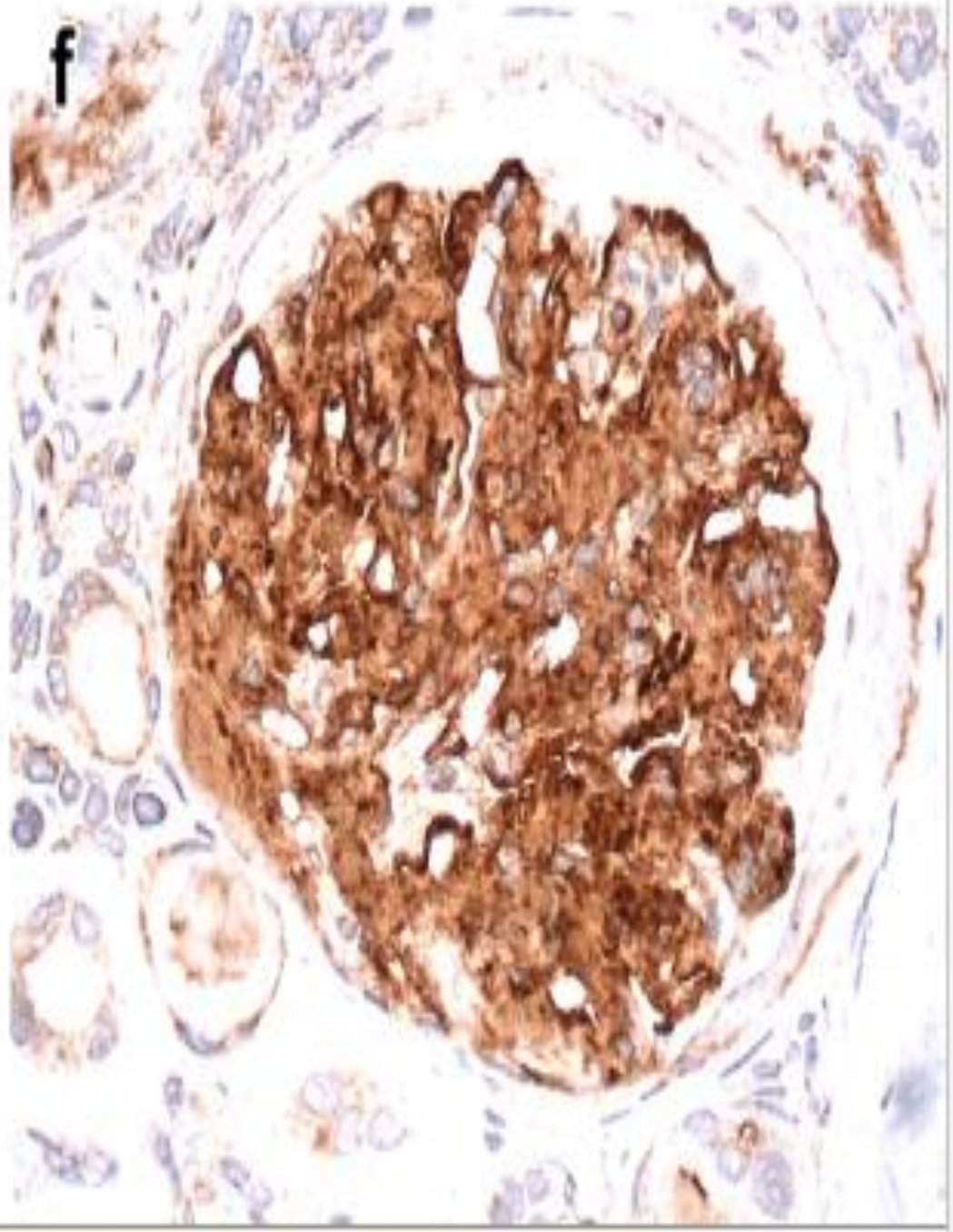
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- **PATHOGENESIS**
- UNTIL RECENTLY, UNDERSTANDING OF THE PATHOGENESIS OF FGN WAS LIMITED, IN PART BECAUSE OF THE LACK OF AN AVAILABLE ANIMAL MODEL FOR THIS CONDITION.

THE OBSERVATION **THAT CRYOGLOBULINEMIC GLOMERULONEPHRITIS CAN APPEAR IDENTICAL AT THE ULTRASTRUCTURAL LEVEL TO FGN, AS WELL AS THE SIMILAR COMPOSITION OF THE DEPOSITS BY IF**, RAISE THE POSSIBILITY OF A **SIMILAR PATHOGENESIS**. THERE IS A SINGLE REPORT OF A PATIENT WITH FGN FOR WHOM SERUM WAS STORED AT 4 °C FOR 4 MONTHS AND THEN RECOVERED.- THE SERUM CONTAINED A CRYOPRECIPITATE THAT DID NOT DISSOLVE UPON REWARMING, SUGGESTING THAT THE **FIBRILS OF FGN MIGHT REPRESENT AN IRREVERSIBLE "SLOW CRYOGLOBULIN."**

A MAJOR BREAKTHROUGH IN OUR UNDERSTANDING OF FGN OCCURRED IN 2018 WHEN 2 INDEPENDENT GROUPS, WORKING AT THE MAYO CLINIC AND THE UNIVERSITY OF WASHINGTON,- UTILIZED **LASER CAPTURE MICRODISSECTION** TO EXTRACT GLOMERULI FROM BIOPSY SPECIMENS OF PATIENTS WITH FGN FOLLOWED BY **LIQUID CHROMATOGRAPHY–ASSISTED TANDEM MASS SPECTROMETRY**. THESE GROUPS SIMULTANEOUSLY **IDENTIFIED DNAJB9 AS ONE OF THE MOST ABUNDANT PROTEINS IN THE FGN GLOMERULAR PROTEOME,** BUT IT WAS NOT PRESENT IN GLOMERULI WITH AMYLOIDOSIS, OTHER FORMS OF GLOMERULONEPHRITIS, OR NORMAL CONTROLS. **DNAJB9 WAS SHOWN TO CO-LOCALIZE WITH IGG AND COMPONENTS OF THE CLASSIC COMPLEMENT PATHWAY IN GLOMERULI**. THESE STUDIES SUGGEST THAT **DNAJB9 MAY ACT AS AN AUTOANTIGEN IN FGN.**

- DNAJB9, ALSO REFERRED TO AS **ERDJ4** (OR **MDG-1**), IS A **223-AMINO ACID** MEMBER OF THE DNAJ FAMILY OF PROTEINS THAT ACT AS **CO-CHAPERONES FOR THE HEAT-SHOCK PROTEIN 70 FAMILY MEMBERS** INCLUDING, MOST NOTABLY, **BINDING IMMUNOGLOBULIN PROTEIN**._ THE **HEAT-SHOCK PROTEIN 70 FAMILY MEMBERS ARE THOUGHT TO BE IMPORTANT CHAPERONES IN THE ENDOPLASMIC RETICULUM (ER), PLAYING A ROLE IN PROTEIN FOLDING, UNFOLDING, TRANSLOCATION, AND DEGRADATION.**

  DNAJB9 FUNCTIONS AS **A CO-CHAPERONE TO BINDING IMMUNOGLOBULIN PROTEIN, ASSISTING IN PROTEIN FOLDING AND THE DEGRADATION OF MISFOLDED PROTEINS, TERMED THE "UNFOLDED PROTEIN RESPONSE."** IN PARTICULAR, DNAJB9 MAY BE IMPORTANT IN THE **RECOGNITION OF MISFOLDED PROTEINS** IN ORDER TO MARK THEM FOR DEGRADATION AND ALSO MAY **INHIBIT THE APOPTOTIC EFFECT OF P53 ON CELLS UNDER CONDITIONS OF CELL STRESS,**- LEADING TO THE **SUGGESTION THAT INCREASED EXPRESSION OF DNAJB9 MAY REPRESENT A MARKER OF INCREASED ER STRESS.**_ **DNAJB9 IS PRESENT AT LOW LEVELS IN THE ER OF MOST CELL TYPES. IN THE NORMAL KIDNEY, DNAJB9 IS PRESENT AT LOW LEVELS IN RENAL TUBULAR EPITHELIAL CELLS, PODOCYTES, AND MESANGIAL AND ENDOTHELIAL CELLS. AT PRESENT, THE ONLY DISEASE KNOWN TO BE ASSOCIATED WITH LARGE AMOUNTS OF *EXTRACELLULAR* DEPOSITION OF DNAJB9 IS FGN.**

- WITH RESPECT TO THE ROLE OF DNAJB9 IN THE DEVELOPMENT OF FGN, **PEPTIDE ANALYSIS HAS DEMONSTRATED THAT THE DNAJB9 DETECTED IN FGN REPRESENTS THE FULL LENGTH, 223-AMINO ACID PROTEIN, AND GENETIC SEQUENCING OF 2 PATIENTS WITH FGN DID NOT REVEAL PATHOGENIC MUTATIONS.**- THE **ABSENCE OF ADDITIONAL COMPONENTS OF ER STRESS PATHWAYS AND UNFOLDED PROTEIN RESPONSE BY MASS SPECTROMETRY ARGUE AGAINST A CENTRAL ROLE OF ER STRESS IN THE PATHOGENESIS OF FGN.- THESE OBSERVATIONS, AS WELL AS THE CO-LOCALIZATION OF DNAJB9 WITH IGG AND COMPONENTS OF THE CLASSIC COMPLEMENT PATHWAY, SUGGEST AN AUTOIMMUNE PATHOGENESIS WITH DNAJB9 ACTING AS THE PUTATIVE AUTOANTIGEN.**DNAJB9 HAS BEEN SHOWN TO BE INDUCIBLE BY THE RAS/RAF/EXTRACELLULAR SIGNAL–REGULATED KINASE PATHWAY IN RESPONSE TO P53, AND SEVERAL KINASE INHIBITORS CURRENTLY IN USE INTERFERE WITH THIS PATHWAY.-

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Article

DNAJB9 Is a Reliable Immunohistochemical Marker of Fibrillary Glomerulonephritis: Evaluation of Diagnostic Efficacy in a Large Series of Kidney Biopsies

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THIS STUDY AIMS TO ASSESS THE DNAJB9 IMMUNOHISTOCHEMICAL EXPRESSION IN A LARGE SERIES OF FGN CASES AND TO EVENTUALLY CONFIRM ITS ROLE AS A DIAGNOSTIC MARKER OF FGN. WE EVALUATED THE IMMUNOHISTOCHEMICAL EXPRESSION OF DNAJB9 (RABBIT POLYCLONAL, THERMOFISHER) IN A SERIES OF 77 FGN AND 128 NON-FGN CASES DIAGNOSED BETWEEN JANUARY 1992 AND JUNE 2022 AT THE PATHOLOGY UNIT OF THE AOU CITTÀ DELLA SALUTE E DELLA SCIENZA HOSPITAL.

DNAJB9 WAS EXPRESSED IN 73 OF THE 74 EVALUABLE FGN CASES, MOSTLY SHOWING A STRONG GLOMERULAR POSITIVITY (68 CASES). DNAJB9 WAS NEGATIVE IN ALL NON-FGN CASES, EVENTUALLY RESULTING IN A **SPECIFICITY OF 100% AND SENSITIVITY OF 99%.** IN CONCLUSION, **WE CONFIRMED THE ROLE OF DNAJB9 AS A DIAGNOSTIC MARKER OF FGN**. ITS ADOPTION IN THE CLINICAL ROUTINE WILL ALLOW A FASTER, MORE FEASIBLE, AND MORE ACCURATE FGN DIAGNOSIS.

IMMUNOTACTOID GLOMERULOPATHY

PATHOLOGY

IMMUNOTACTOID GLOMERULOPATHY, IN CONTRAST TO FIBRILLARY GLOMERULONEPHRITIS, IS CHARACTERIZED BY THE FORMATION OF **MICROTUBULES** ON ELECTRON MICROSCOPY. IN ADDITION, THESE MICROTUBULES ARE TYPICALLY **MUCH LARGER** THAN THE FIBRILS IN FIBRILLARY GLOMERULONEPHRITIS (**17 TO 52** VERSUS 16 TO 24 NM IN DIAMETER) HOWEVER, DUE TO THE **OVERLAP**, SUBSTRUCTURE DIAMETER ALONE IS INSUFFICIENT TO DISTINGUISH BETWEEN FIBRILLARY GLOMERULONEPHRITIS AND IMMUNOTACTOID GLOMERULOPATHY. IMMUNOSTAINING FOR THE **MARKER DNAJB9**, WHICH IS POSITIVE AMONG PATIENTS WITH FIBRILLARY GLOMERULONEPHRITIS, IS **UNIFORMLY NEGATIVE**.

MOST PATIENTS HAVE **EITHER A CIRCULATING PARAPROTEIN OR MONOCLONAL IMMUNOGLOBULIN DEPOSITION IN THE GLOMERULI ON IMMUNOFLUORESCENCE MICROSCOPY WITH A RESTRICTED LIGHT CHAIN, EITHER KAPPA OR LAMBDA**. DEPOSITS ARE **ALMOST ALWAYS COMPOSED OF IGG** (PREDOMINANTLY **IGG1** OR **IGG2**).

- **●PATHOGENESIS**

  MOST CASES OF IMMUNOTACTOID GLOMERULOPATHY ARE ASSOCIATED WITH A **LYMPHOCYTIC OR PLASMA CELL DISORDER**, EITHER I**NDOLENT** ACCORDING TO HEMATOLOGIC CRITERIA (AND **CORRESPONDING TO MONOCLONAL GAMMOPATHY OF RENAL SIGNIFICANCE**) OR **SYMPTOMATIC**. SOME AUTHORS CALL THIS DISORDER GLOMERULONEPHRITIS WITH ORGANIZED MONOCLONAL MICROTUBULAR IMMUNOGLOBULIN DEPOSITS (**GOMMID**) TUBULOINTERSTITIAL INFILTRATION WITH MALIGNANT B CELLS MAY BE OBSERVED IN PATIENTS WITH IMMUNOTACTOID GLOMERULOPATHY ASSOCIATED WITH SYMPTOMATIC CHRONIC LYMPHOCYTIC LEUKEMIA OR B CELL LYMPHOMA. **THE ABSENCE OF DETECTABLE CIRCULATING CRYOGLOBULINS IS REQUIRED TO ESTABLISH THE DIAGNOSIS OF IMMUNOTACTOID GLOMERULOPATHY.**

- IN A STUDY OF 14 PATIENTS WITH IMMUNOTACTOID GLOMERULOPATHY, GLOMERULAR DEPOSITS WERE COMPOSED OF MONOTYPIC IGG IN 13 PATIENTS WHO ALSO HAD A **MONOCLONAL** IMMUNOGLOBULIN OF THE SAME ISOTYPE IN THE SERUM AND/OR THE CYTOPLASM OF LYMPHOCYTES .IN ADDITION, A LYMPHOPROLIFERATIVE DISEASE WAS OBSERVED IN SEVEN PATIENTS. BY COMPARISON, NONE OF NINE PATIENTS WITH FIBRILLARY GLOMERULONEPHRITIS HAD A PARAPROTEIN OR A LYMPHOPROLIFERATIVE DISORDER, WHILE EIGHT OF THE NINE PATIENTS HAD **POLYCLONAL** IMMUNOGLOBULIN GLOMERULAR DEPOSITS.
- THUS, **A CAREFUL SEARCH FOR A B CELL OR PLASMA CELL LYMPHOPROLIFERATIVE DISEASE SHOULD BE PART OF THE ROUTINE EVALUATION OF PATIENTS WITH IMMUNOTACTOID GLOMERULOPATHY**.

- **CLINICAL FEATURES**
- THE PRESENTING CLINICAL FEATURES OF FIBRILLARY GLOMERULONEPHRITIS AND IMMUNOTACTOID GLOMERULOPATHY ARE SIMILAR TO THOSE IN OTHER FORMS OF GLOMERULAR DISEASE.
  THE LARGEST REPORTED EXPERIENCE DESCRIBED THE CLINICAL FEATURES IN 186 PATIENTS WITH FIBRILLARY GLOMERULONEPHRITIS OR IMMUNOTACTOID GLOMERULOPATHY. APPROXIMATELY 90 PERCENT OF PATIENTS HAD FIBRILLARY GLOMERULONEPHRITIS, BUT THE CLINICAL FINDINGS WERE SIMILAR IN BOTH DISORDERS. BOTH AFFECT MIDDLE-AGED INDIVIDUALS, WITH THE REPORTED AGE AT DIAGNOSIS RANGING FROM 41 TO 80 YEARS.

-THE FOLLOWING FINDINGS WERE NOTED AT PRESENTATION:

●HEMATURIA IN 70 PERCENT

●PROTEINURIA IN 100 PERCENT, WITH NEPHROTIC SYNDROME (PROTEIN EXCRETION ≥3.5 G/DAY) IN 70 TO 75 PERCENT

●KIDNEY FUNCTION IMPAIRMENT (SERUM CREATININE ≥1.5 MG/DL [133 MICROMOL/L]) IN 50 TO 55 PERCENT

●HYPERTENSION IN 65 TO 70 PERCENT

●MONOCLONAL GAMMOPATHY IN 16 TO 63 PERCENT

- A SIMILAR SPECTRUM OF FINDINGS WAS REPORTED IN TWO INDEPENDENT SERIES OF IMMUNOTACTOID GLOMERULOPATHY. IN BOTH OF THESE STUDIES, 33 PERCENT OF PATIENTS HAD HYPOCOMPLEMENTEMIA.

ASSOCIATED DISEASES MOST CASES OF FIBRILLARY GLOMERULONEPHRITIS WERE PREVIOUSLY CONSIDERED IDIOPATHIC. HOWEVER, 30 TO 50 PERCENT OF CASES OF FIBRILLARY GLOMERULONEPHRITIS ARE ASSOCIATED WITH MALIGNANCY, MONOCLONAL GAMMOPATHY, AUTOIMMUNE DISEASE, OR INFECTIONS.

THE FREQUENCY WITH WHICH THESE ASSOCIATED DISORDERS OCCUR WAS ILLUSTRATED IN A REPORT OF 66 PATIENTS WITH FIBRILLARY GLOMERULONEPHRITIS :

FIFTEEN PATIENTS (23 PERCENT) HAD AN ASSOCIATED MALIGNANCY, WHICH WAS DIAGNOSED 15 YEARS BEFORE TO 10 YEARS AFTER THE ONSET OF KIDNEY DISEASE. SIX OF THE 15 MALIGNANCIES WERE DUE TO **MULTIPLE MYELOMA OR LEUKEMIA**.

ELEVEN PATIENTS (17 PERCENT) HAD A **MONOCLONAL GAMMOPATHY**, WHICH IS SIMILAR TO THE 15 PERCENT INCIDENCE REPORTED IN ANOTHER STUDY. HOWEVER, SUBSEQUENT STUDIES HAVE FOUND THAT **THE VAST MAJORITY OF CASES OF DNAJB9-POSITIVE FIBRILLARY GLOMERULONEPHRITIS ARE NOT ASSOCIATED WITH MONOCLONAL GAMMOPATHY, WHEREAS RARE CASES OF DNAJB9-NEGATIVE FIBRILLARY GLOMERULONEPHRITIS (<2 PERCENT) APPEAR TO BE ASSOCIATED WITH A MONOCLONAL GAMMOPATHY OF RENAL SIGNIFICANCE** . WHETHER THESE RARE DNAJB9-NEGATIVE CASES ARE TRULY FIBRILLARY GLOMERULONEPHRITIS IS QUESTIONABLE. TEN PATIENTS (15 PERCENT) HAD AUTOIMMUNE DISORDERS (MOST OFTEN **CROHN DISEASE, LUPUS, GRAVES' DISEASE, AND IMMUNE THROMBOCYTOPENIA [ITP]).**

- CASES OF FIBRILLARY GLOMERULONEPHRITIS ASSOCIATED WITH **SJÖGREN'S DISEASE , RHEUMATOID ARTHRITIS, BEHÇET SYNDROME, IMMUNE CHECKPOINT INHIBITOR THERAPY, AND COVID-19 VACCINATION** ,HAVE ALSO BEEN DESCRIBED.
- BY CONTRAST, **IMMUNOTACTOID GLOMERULOPATHY IS MORE FREQUENTLY ASSOCIATED WITH CHRONIC LYMPHOCYTIC LEUKEMIA AND RELATED B CELL LYMPHOMAS OR MULTIPLE MYELOMA**. IN THE LARGEST SERIES OF 73 PATIENTS, 48 (66 PERCENT) HAD A HEMATOLOGIC DISORDER, INCLUDING LYMPHOMA IN 41 PERCENT (MAINLY CHRONIC LYMPHOCYTIC LEUKEMIA/SMALL LYMPHOCYTIC LYMPHOMA), MONOCLONAL GAMMOPATHY IN 20 PERCENT, AND MULTIPLE MYELOMA IN 6 PERCENT. PATIENTS WITH IMMUNOTACTOID GLOMERULOPATHY AND MONOCLONAL DEPOSITS IN THE KIDNEY HAD A MUCH HIGHER INCIDENCE OF HEMATOLOGIC DISORDERS THAN THOSE WITH POLYCLONAL DEPOSITS.
- BOTH FIBRILLARY GLOMERULONEPHRITIS AND IMMUNOTACTOID GLOMERULOPATHY HAVE BEEN DESCRIBED IN PATIENTS WITH HEPATITIS C VIRUS (HCV) INFECTION. FIBRILLARY GLOMERULONEPHRITIS HAS BEEN ALSO DESCRIBED IN ASSOCIATION WITH ANTI-GLOMERULAR BASEMENT MEMBRANE DISEASE.

- **DIAGNOSIS**

THE DIAGNOSIS OF FIBRILLARY GLOMERULONEPHRITIS OR IMMUNOTACTOID GLOMERULOPATHY IS MADE BY KIDNEY BIOPSY IN A PATIENT WITH SUSPECTED GLOMERULAR DISEASE.

FIBRILLARY GLOMERULONEPHRITIS CAN BE DISTINGUISHED FROM IMMUNOTACTOID GLOMERULOPATHY ON THE BASIS **OF ELECTRON MICROSCOPY** AS WELL AS POSITIVE **IMMUNOFLUORESCENCE STAINING FOR DNAJB9**. THERE ARE NO ESTABLISHED, NONINVASIVE LABORATORY TESTS TO DIAGNOSE FIBRILLARY GLOMERULONEPHRITIS OR IMMUNOTACTOID GLOMERULOPATHY. HOWEVER, ONE STUDY FOUND THAT SERUM LEVELS OF DNAJB9 WERE FOURFOLD HIGHER IN PATIENTS WITH FIBRILLARY GLOMERULONEPHRITIS COMPARED WITH HEALTHY CONTROLS AND PATIENTS WITH MULTIPLE MYELOMA, IMMUNOGLOBULIN LIGHT CHAIN (AL) AMYLOIDOSIS, AND OTHER GLOMERULAR DISEASES (INCLUDING IMMUNOTACTOID GLOMERULOPATHY .

SERUM DNAJB9 LEVELS PREDICTED A DIAGNOSIS OF FIBRILLARY GLOMERULONEPHRITIS WITH A SENSITIVITY AND SPECIFICITY OF 67 AND 98 PERCENT, RESPECTIVELY. THESE FINDINGS SUGGEST THAT **DNAJB9 COULD BE USEFUL AS A SERUM BIOMARKER FOR THE DIAGNOSIS OF FIBRILLARY GLOMERULONEPHRITIS**, ALTHOUGH VALIDATION IN LARGER, PROSPECTIVE STUDIES IS NEEDED. TESTING FOR SERUM DNAJB9 IS NOT YET COMMERCIALLY AVAILABLE.

PATIENTS WITH A DIAGNOSIS OF FIBRILLARY GLOMERULONEPHRITIS SHOULD BE **SCREENED FOR MALIGNANCY, MONOCLONAL GAMMOPATHY, AUTOIMMUNE DISEASE, AND HCV INFECTION** .THE TEMPORAL RELATIONSHIP WITH THESE DISEASES IS VARIABLE. AS AN EXAMPLE, MALIGNANCY MAY PRECEDE, BE CONCOMITANT WITH, OR FOLLOW THE DIAGNOSIS BY MANY YEARS. THUS, **ONGOING MONITORING IS WARRANTED IN THESE PATIENTS**. WE PERFORM THE FOLLOWING TESTS AT THE TIME THE KIDNEY DISEASE IS DIAGNOSED:

- **COMPLETE BLOOD COUNT** WITH DIFFERENTIAL (SHOULD BE REPEATED AT LEAST ANNUALLY)
- SERUM AND URINE PROTEIN **ELECTROPHORESIS** WITH **IMMUNOFIXATION** AND **SERUM FREE LIGHT CHAINS** (SHOULD BE REPEATED AT LEAST ANNUALLY)
- TESTS FOR **HCV AND HIV**
- ANTINUCLEAR ANTIBODY (**ANA**) AND, **IF POSITIVE, ANTI-DOUBLE STRANDED DNA (ANTI-DSDNA), ANTI-SM, ANTI-RO/SSA, AND ANTI-LA/SSB**
- **C3 AND C4** COMPLEMENT LEVELS
- **CRYOGLOBULINS**
- **CHEST RADIOGRAPH**

- PATIENTS WITHOUT KNOWN CANCER WHO ARE DIAGNOSED WITH FIBRILLARY GLOMERULONEPHRITIS SHOULD UNDERGO AGE- AND RISK-APPROPRIATE CANCER SCREENING, IF NOT ALREADY PERFORMED.

- PATIENTS WITH A DIAGNOSIS OF IMMUNOTACTOID GLOMERULOPATHY SHOULD BE SCREENED FOR MONOCLONAL GAMMOPATHY WITH SERUM AND URINE ELECTROPHORESIS WITH IMMUNOFIXATION AND SERUM FREE LIGHT CHAIN LEVELS. IN THOSE WITH CONFIRMED MONOTYPIC DEPOSITS AND/OR MONOCLONAL GAMMOPATHY, ADDITIONAL INVESTIGATIONS MAY BE REQUIRED TO CHARACTERIZE THE NATURE OF THE UNDERLYING CLONAL DISORDER, INCLUDING BONE MARROW EXAMINATION WITH FLOW CYTOMETRY, AND, WHEN A B CELL LYMPHOPROLIFERATIVE DISEASE IS SUSPECTED, FLOW CYTOMETRY OF BLOOD LYMPHOCYTES; COMPUTED TOMOGRAPHY (CT) SCAN OF THE CHEST, ABDOMEN, AND PELVIS; AND/OR POSITRON EMISSION TOMOGRAPHY (PET) SCAN.

- **TREATMENT**

- FIBRILLARY AND IMMUNOTACTOID GLOMERULAR DISEASE ARE DIFFICULT TO TREAT AND THERE ARE NO RANDOMIZED CONTROLLED TRIALS TO GUIDE OPTIMAL THERAPY. ALTHOUGH WE CONSIDER THESE DISORDERS TO BE TWO PATHOLOGICALLY DISTINCT PROCESSES, OUR APPROACH TO TREATMENT IN PATIENTS **WITHOUT A SECONDARY CAUSE** IS SIMILAR FOR BOTH AND IS BASED PRIMARILY UPON THE LIMITED AVAILABLE DATA FROM RETROSPECTIVE STUDIES AND CASE SERIES AND OUR OWN CLINICAL EXPERIENCE. THERE ARE **NO** THERAPIES THAT HAVE BEEN CLEARLY SHOWN TO BE BENEFICIAL FOR EITHER FIBRILLARY GLOMERULONEPHRITIS OR IMMUNOTACTOID GLOMERULOPATHY. PATIENTS WHO HAVE A POSSIBLE SECONDARY CAUSE FOR THESE DISORDERS, SUCH AS MALIGNANCY, MONOCLONAL GAMMOPATHY, INFECTION, OR AUTOIMMUNE DISEASE, MAY BENEFIT FROM TREATMENT OF THE UNDERLYING DISORDER. THIS IS ESPECIALLY TRUE FOR PATIENTS WITH A MONOCLONAL GAMMOPATHY WHO MAY BENEFIT FROM B CELL OR PLASMA CELL TARGETED THERAPY. IN PATIENTS WITH IDIOPATHIC DISEASE, OUR APPROACH TO TREATMENT IS GENERALLY DETERMINED BY THE SEVERITY OF KIDNEY DYSFUNCTION.

- **PATIENTS WITH SECONDARY CAUSES** IN PATIENTS WITH FIBRILLARY GLOMERULONEPHRITIS WHO HAVE AN ASSOCIATED MALIGNANCY OR AUTOIMMUNE DISORDER, WE ADVOCATE FOR TREATMENT OF THESE CONDITIONS AS APPROPRIATE IN CONSULTATION WITH A HEMATOLOGIST/ONCOLOGIST OR RHEUMATOLOGIST, RESPECTIVELY.
- IN PATIENTS WITH **FIBRILLARY** GLOMERULONEPHRITIS OR IMMUNOTACTOID GLOMERULOPATHY WHO HAVE AN ASSOCIATED MONOCLONAL GAMMOPATHY (IE, PATIENT HAS MONOTYPIC DEPOSITS ON IMMUNOFLUORESCENCE STAINING OF THE KIDNEY BIOPSY OR A DETECTABLE SERUM OR URINE MONOCLONAL PROTEIN) WITH OR WITHOUT A DETECTABLE PLASMA OR B CELL CLONE, WE TREAT WITH **THERAPY DIRECTED AGAINST THE PATHOLOGIC CLONE RESPONSIBLE FOR THE MONOCLONAL GAMMOPATHY** . THIS APPROACH IS SIMILAR TO THAT USED FOR PATIENTS WITH PROLIFERATIVE GLOMERULONEPHRITIS WITH MONOCLONAL IMMUNOGLOBULIN DEPOSITS (PGNMID) ,
- IN PATIENTS WITH **IMMUNOTACTOID** GLOMERULOPATHY WHO HAVE AN ASSOCIATED **MONOCLONAL GAMMOPATHY BUT NO DETECTABLE PLASMA OR B CELL CLONE,** TREATMENT WITH **RITUXIMAB-BASED** THERAPY TO ERADICATE A "HYPOTHESIZED B CELL CLONE" IS A POTENTIAL INITIAL OPTION, GIVEN THE HIGH INCIDENCE OF UNDERLYING B CELL DISORDERS IN IMMUNOTACTOID GLOMERULOPATHY . THERE IS ONE CASE REPORT OF SUCCESSFUL TREATMENT WITH **BORTEZOMIB**-BASED THERAPY .

●IN PATIENTS WITH FIBRILLARY GLOMERULONEPHRITIS OR IMMUNOTACTOID GLOMERULOPATHY WHO HAVE **CHRONIC HCV INFECTION** AND HAVE NOT YET RECEIVED THERAPY, WE ADVOCATE FOR TREATMENT OF HCV AS APPROPRIATE. HOWEVER, EVIDENCE THAT TREATING HCV INFECTION RESULTS IN IMPROVEMENT OF FIBRILLARY GLOMERULONEPHRITIS IS LACKING.

- IN ADDITION TO ADDRESSING THE UNDERLYING DISORDER, WE ADMINISTER THERAPIES AIMED AT **REDUCING PROTEINURIA, CONTROLLING BLOOD PRESSURE, AND SLOWING THE PROGRESSION OF KIDNEY DISEASE**, AS DISCUSSED BELOW. PATIENTS SHOULD BE ROUTINELY MONITORED DURING TREATMENT FOR SIGNS OF KIDNEY DISEASE PROGRESSION. WE TYPICALLY **MONITOR SERUM CREATININE CONCENTRATION AND URINE PROTEIN EXCRETION EVERY THREE TO SIX MONTHS**. IF PATIENTS DO NOT SHOW SIGNS OF IMPROVEMENT OF THEIR KIDNEY DISEASE FOLLOWING TREATMENT OF THE UNDERLYING DISORDER, TREATMENT WITH **IMMUNOSUPPRESSIVE** THERAPY CAN BE CONSIDERED ON A CASE-BY-CASE BASIS.

- **PATIENTS WITH IDIOPATHIC DISEASE** IN PATIENTS WITH FIBRILLARY GLOMERULONEPHRITIS OR IMMUNOTACTOID GLOMERULOPATHY WHO DO NOT HAVE A SECONDARY CAUSE OF THEIR KIDNEY DISEASE, OUR APPROACH TO TREATMENT **DEPENDS UPON THE SEVERITY OF THEIR KIDNEY DISEASE.**
- **ESTIMATED GFR ≥60 ML/MIN/1.73 M2 AND PROTEINURIA <3.5 G/DAY** IN PATIENTS WITH RELATIVELY PRESERVED KIDNEY FUNCTION (ESTIMATED GLOMERULAR FILTRATION RATE [EGFR] OF ≥60 ML/MIN/1.73 M^2) AND SUBNEPHROTIC-RANGE PROTEINURIA (<3.5 G/DAY), WE PREFER A **MORE CONSERVATIVE** INITIAL APPROACH TO TREATMENT. WE TREAT THESE PATIENTS WITH ANTIPROTEINURIC THERAPY (ANGIOTENSIN-CONVERTING ENZYME [**ACE**] **INHIBITORS OR ANGIOTENSIN RECEPTOR BLOCKERS** [**ARBS**]), **BLOOD PRESSURE CONTROL, AND DIETARY SODIUM RESTRICTION** INDEFINITELY. IN ADDITION, WE ADMINISTER **LIPID-LOWERING** THERAPY AS APPROPRIATE FOR PATIENTS WITH HYPERLIPIDEMIA AND ADVOCATE **WEIGHT REDUCTION** IN PATIENTS WHO ARE OVERWEIGHT OR OBESE.

  WE MONITOR THE PATIENT BY OBTAINING SERUM **CREATININE CONCENTRATION AND URINE PROTEIN EXCRETION EVERY THREE TO SIX MONTHS**. IN PATIENTS WHO RESPOND TO CONSERVATIVE THERAPY (IE, PROTEINURIA DECREASES AND SERUM CREATININE AND EGFR REMAIN STABLE), WE CONTINUE THESE MEASURES AND MONITOR THE PATIENT CLOSELY FOR SIGNS OF DISEASE PROGRESSION. **PATIENTS WHO DEVELOP PROGRESSIVE LOSS OF KIDNEY FUNCTION OR WORSENING PROTEINURIA DESPITE MAXIMAL CONSERVATIVE THERAPY SHOULD BE CONSIDERED FOR IMMUNOSUPPRESSIVE THERAPY.**

- **ESTIMATED GFR <60 ML/MIN/1.73 M2 OR PROTEINURIA >3.5 G/DAY** THERE ARE NO RANDOMIZED TRIALS TO GUIDE THE OPTIMAL THERAPY IN PATIENTS WITH FIBRILLARY GLOMERULONEPHRITIS OR IMMUNOTACTOID GLOMERULOPATHY WHO HAVE ABNORMAL KIDNEY FUNCTION (ESTIMATED GLOMERULAR FILTRATION RATE [EGFR] <60 ML/MIN/1.73 M^2) OR NEPHROTIC RANGE PROTEINURIA (>3.5 G/DAY), AND **NO IMMUNOSUPPRESSIVE THERAPIES HAVE BEEN CLEARLY SHOWN TO BE BENEFICIAL**. HOWEVER, GIVEN THE GENERALLY POOR PROGNOSIS ASSOCIATED WITH THESE DISORDERS, IT IS REASONABLE TO OFFER A TRIAL OF IMMUNOSUPPRESSIVE THERAPY AFTER DISCUSSING THE POTENTIAL RISKS AND BENEFITS OF TREATMENT WITH THE PATIENT. WE PREFER THE USE OF RITUXIMAB, ADMINISTERED EITHER AS **FOUR WEEKLY DOSES OF 375 MG/M^2 INTRAVENOUSLY (IV) OR AS 1 G IV INITIALLY FOLLOWED 14 DAYS LATER BY ANOTHER 1 G DOSE**, BASED UPON OBSERVATIONAL DATA SUGGESTING A BENEFIT IN SOME PATIENTS. IN ADDITION, WE ADMINISTER **CONSERVATIVE** MEASURES USED TO CONTROL BLOOD PRESSURE AND REDUCE PROTEIN EXCRETION FOR THE DURATION OF THE DISEASE.

WE MONITOR THE PATIENT BY **OBTAINING SERUM CREATININE CONCENTRATION AND URINE PROTEIN EXCRETION EVERY THREE TO SIX MONTHS**. IN PATIENTS WHO RESPOND TO RITUXIMAB THERAPY (IE, PROTEINURIA DECREASES AND/OR SERUM CREATININE AND EGFR REMAIN STABLE), WE CONTINUE

MONITORING THE PATIENT FOR SIGNS OF DISEASE PROGRESSION EVERY THREE TO SIX MONTHS. **IF PROTEINURIA DECREASES BUT THE PATIENT DOES NOT GO INTO COMPLETE REMISSION (IE, PROTEINURIA <300 MG/24 HOURS) AFTER A MINIMUM OF SIX MONTHS FOLLOW-UP**, WE **MEASURE THE PATIENT'S B CELL COUNTS (CD19-POSITIVE** CELLS BY FLOW CYTOMETRIC ANALYSIS)

IF **THE CD19-POSITIVE B CELL COUNT** IS **>5 PER MICROL**, WE **REDOSE THE PATIENT WITH A SINGLE DOSE OF RITUXIMAB 1 G IV.** IF, **AFTER THE SECOND COURSE OF RITUXIMAB, PROTEINURIA STABILIZES BUT THE PATIENT DOES NOT ACHIEVE COMPLETE REMISSION, WE ASSUME THAT RESIDUAL PROTEINURIA IS DUE TO CHRONIC DAMAGE AND CONTINUE CONSERVATIVE THERAPY WITHOUT REDOSING RITUXIMAB. IN PATIENTS WHO DO NOT RESPOND TO RITUXIMAB THERAPY, WE TYPICALLY DO NOT OFFER ADDITIONAL IMMUNOSUPPRESSIVE THERAPY, SINCE THE RISKS OF TREATMENT (EG, INFECTION, MALIGNANCY) LIKELY OUTWEIGH ANY POTENTIAL BENEFITS.**

- SOME BUT NOT ALL REPORTS SUGGEST THAT RITUXIMAB MAY BE ASSOCIATED WITH COMPLETE OR PARTIAL REMISSION OF PROTEINURIA IN PATIENTS WITH FIBRILLARY GLOMERULONEPHRITIS.
- RITUXIMAB ALSO APPEARED TO BE EFFECTIVE IN A CASE REPORT OF RECURRENT IMMUNOTACTOID GLOMERULOPATHY IN THE TRANSPLANT THAT HAD NOT RESPONDED TO CONVENTIONAL IMMUNOSUPPRESSIVE THERAPY.
- IMMUNOSUPPRESSIVE THERAPY WITH **GLUCOCORTICOIDS** WITH OR WITHOUT OTHER AGENTS (EG, CYCLOPHOSPHAMIDE, MYCOPHENOLATE MOFETIL, CYCLOSPORINE, MELPHALAN, AZATHIOPRINE, AND RAPAMYCIN) HAS BEEN REPORTED IN UNCONTROLLED STUDIES **WITH LIMITED AND INCONSISTENT RESULTS.**

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Treatment of fibrillary glomerulonephritis with rituximab: a 12-month pilot study

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METHODS. THIS WAS A PILOT PROSPECTIVE CLINICAL TRIAL IN WHICH PATIENTS WITH IDIOPATHIC FGN WERE TREATED WITH TWO COURSES OF RITUXIMAB (1 G EACH) 2 WEEKS APART AT THE BEGINNING AND THEN AGAIN AT 6MONTHS. **PRIMARY OUTCOME WAS DEFINED AS PRESERVATION OF KIDNEY FUNCTION AT 12MONTHS WITH STABLE OR INCREASED CREATININE CLEARANCE. SECONDARY OUTCOME WAS DEFINED AS ACHIEVING COMPLETE REMISSION (CR) DEFINED AS PROTEINURIA <300MG/24 H OR PARTIAL REMISSION (PR) WITH PROTEINURIA <3 G/24H AND AT LEAST 50% REDUCTION IN THE PROTEINURIA. DNAJB9** LEVELS WERE ALSO MEASURED IN THE SERUM **AT BASELINE, 6 AND 12MONTHS**.

RESULTS. THE CREATININE CLEARANCE DID NOT CHANGE SIGNIFICANTLY DURING THIS TIME, FROM 47.7ML/MIN/1.73M2 AT BASELINE TO 43.7ML/MIN/1.73M2 DURING FOLLOW-UP. PROTEINURIA DECLINED FROM 4.43 (1.6–5.53) G/24 H AT BASELINE TO 1.9 (0.46-5.26) G/24 H AT 12MONTHS BUT DID NOT REACH SIGNIFICANCE .NONE OF THE PATIENTS REACHED CR, AND 3 OF THE 11 ACHIEVED PR. THERE WAS NO CHANGE IN THE DNAJB9 LEVELS FOLLOWING TREATMENT WITH RITUXIMAB. THE MOST COMMON ADVERSE EVENT WAS NASAL CONGESTION, FATIGUE AND MUSCLE CRAMPS.

CONCLUSIONS. TREATMENT OF PATIENTS WITH TWO COURSES OF RITUXIMAB OVER A SPAN OF 6MONTHS WAS ASSOCIATED WITH **STABILIZATION OF RENAL FUNCTION BUT DID NOT RESULT IN A SIGNIFICANT CHANGE IN PROTEINURIA AND WITH NO CHANGE IN THE DNAJB9 LEVELS.**

- **END-STAGE KIDNEY DISEASE** DIALYSIS OR KIDNEY TRANSPLANTATION CAN BE PERFORMED IN PATIENTS WITH FIBRILLARY GLOMERULONEPHRITIS OR IMMUNOTACTOID GLOMERULOPATHY WHO PROGRESS TO ESKD. **WITH KIDNEY TRANSPLANTATION, RECURRENT DISEASE CAN DEVELOP IN THE ALLOGRAFT IN BOTH DISORDERS, BUT THE RATE OF PROGRESSION IS USUALLY SLOWER THAN IN THE NATIVE KIDNEY**. THE RATE OF **RECURRENCE APPEARS BE HIGHER IN PATIENTS WHO HAVE A MONOCLONAL GAMMOPATHY**, WHICH OCCURS IN BOTH DISORDERS.
- A STUDY FROM THE AUSTRALIA AND NEW ZEALAND DIALYSIS AND TRANSPLANT REGISTRY REPORTED THE PROGNOSIS OF 55 PATIENTS WITH ESKD DUE TO FIBRILLARY GLOMERULONEPHRITIS AND 11 PATIENTS WITH IMMUNOTACTOID GLOMERULOPATHY. PATIENTS WITH FIBRILLARY GLOMERULONEPHRITIS HAD SURVIVAL RATES ON DIALYSIS THAT WERE COMPARABLE WITH THOSE OF PATIENTS WITH OTHER CAUSES OF ESKD. HOWEVER, PATIENTS WITH IMMUNOTACTOID GLOMERULOPATHY HAD INFERIOR SURVIVAL ON DIALYSIS. AMONG PATIENTS WHO WERE TRANSPLANTED, RECURRENT DISEASE OCCURRED IN 1 OF 13 PATIENTS WITH FIBRILLARY GLOMERULONEPHRITIS AND 1 OF 4 PATIENTS WITH IMMUNOTACTOID GLOMERULOPATHY.

- IN A REPORT OF TWO PATIENTS WITH IMMUNOTACTOID GLOMERULOPATHY WHO UNDERWENT KIDNEY TRANSPLANTATION PLUS TWO OTHERS IN CASE REPORTS, TWO DEVELOPED RECURRENT DISEASE AT TWO- TO SIX-YEAR FOLLOW-UP. IN **OTHER CASE REPORTS OF IMMUNOTACTOID GLOMERULOPATHY, MORE AGGRESSIVE IMMUNOSUPPRESSIVE THERAPY (INCLUDING PLASMA EXCHANGE, PULSE METHYLPREDNISOLONE, AND CYCLOPHOSPHAMIDE PULSES RATHER THAN AZATHIOPRINE) OR THE USE OF RITUXIMAB APPEARED TO BE BENEFICIAL.**

- IN SUMMARY, **KIDNEY TRANSPLANTATION IS A REASONABLE THERAPEUTIC OPTION FOR PATIENTS WITH FIBRILLARY GLOMERULONEPHRITIS WHO DEVELOP ESKD. IN THOSE WITH AN ASSOCIATED MONOCLONAL GAMMOPATHY, A THOROUGH EVALUATION OF THE MONOCLONAL GAMMOPATHY SHOULD BE ADDRESSED PRIOR TO TRANSPLANTATION.**

  IMMUNOTACTOID GLOMERULOPATHY MAY RECUR IN THE KIDNEY ALLOGRAFT AND MAY RESULT IN LOSS OF THE ALLOGRAFT. IN PATIENTS WITH **MONOCLONAL IMMUNOTACTOID GLOMERULOPATHY, TREATMENT OF THE MONOCLONAL GAMMOPATHY SHOULD BE ADDRESSED PRIOR TO TRANSPLANTATION.**

- **OTHER FIBRILLARY DISORDERS** UNLIKE FIBRILLARY GLOMERULONEPHRITIS AND IMMUNOTACTOID GLOMERULOPATHY, OTHER NONAMYLOID FIBRILLARY GLOMERULAR DISEASES HAVE BEEN DESCRIBED IN WHICH **STAINING FOR IMMUNOGLOBULINS IS NEGATIVE**.
- **FIBRONECTIN GLOMERULOPATHY** FIBRONECTIN GLOMERULOPATHY IS AN **AUTOSOMAL DOMINANT** DISORDER ASSOCIATED WITH **MASSIVE DEPOSITION OF FIBRONECTIN. IT PRESENTS WITH PROTEINURIA, OFTEN IN THE NEPHROTIC RANGE,** IN THE **THIRD TO FOURTH DECADE** AND **SLOWLY PROGRESSES TO END-STAGE KIDNEY DISEASE** (ESKD). FIBRONECTIN GLOMERULOPATHY MAY RECUR AFTER KIDNEY TRANSPLANTATION.
- **COLLAGENOFIBROTIC GLOMERULOPATHY** COLLAGENOFIBROTIC GLOMERULOPATHY, ALSO CALLED **COLLAGEN TYPE III GLOMERULOPATHY,** IS A RARE DISORDER THAT IS CHARACTERIZED BY THE **MASSIVE ACCUMULATION OF ATYPICAL TYPE III COLLAGEN FIBRILS IN THE MESANGIUM AND SUBENDOTHELIAL** SPACE. LIGHT MICROSCOPY REVEALS FINDINGS CONSISTENT WITH **MEMBRANOPROLIFERATIVE GLOMERULONEPHRITIS**, INCLUDING A DOUBLE-CONTOUR APPEARANCE OF THE PERIPHERAL CAPILLARY WALLS**. A DEFINITIVE DIAGNOSIS REQUIRES ELECTRON MICROSCOPY, WHICH REVEALS FIBERS WITH A TRANSVERSE BAND STRUCTURE** AND A DISTINCTIVE PERIODICITY OF APPROXIMATELY **60 NM**. THIS IS THE SAME AS THAT OBSERVED WITH TYPE III COLLAGEN.
- CONTROVERSY EXISTS AS TO WHETHER COLLAGENOFIBROTIC GLOMERULOPATHY IS A PRIMARY DISEASE OF THE KIDNEY OR A SYSTEMIC PROCESS. **MARKED ELEVATIONS IN SERUM TYPE III PROCOLLAGEN PEPTIDE** LEVELS ARE OBSERVED. SOME CASES HAVE BEEN DESCRIBED IN FAMILIES, SUGGESTING AN **AUTOSOMAL RECESSIVE** DISORDER.
- AFFECTED PATIENTS TYPICALLY PRESENT WITH **PROTEINURIA AND EDEMA, WITH FREQUENT PROGRESSION TO ESKD**. THERE IS **NO SPECIFIC THERAPY.**

- **OTHER**

PATIENTS WITH **NAIL-PATELLA SYNDROME** AND **HEREDITARY MULTIPLE EXOSTOSES SYNDROME** (ALSO CALLED **HEREDITARY MULTIPLE OSTEOCHONDROMAS SYNDROME**) MAY DEVELOP **NEPHROTIC SYNDROME** ASSOCIATED WITH GLOMERULAR **FIBRILLAR COLLAGEN DEPOSITION** .

FIBRILS CAN ALSO BE SEEN IN PATIENTS WITH **DIABETIC GLOMERULOSCLEROSIS**, A RARE CONDITION KNOWN AS **DIABETIC FIBRILLOSIS** . WITHIN THE KIDNEY, THESE FIBRILS ARE LOCALIZED TO THE **MESANGIUM**, ARE **SEGMENTAL** IN FASHION, AND ARE **BUNDLE-LIKE AND NOT RANDOMLY** ARRANGED. IMMUNOFLUORESCENCE STAINING FOR DNAJ HEAT SHOCK PROTEIN FAMILY (HSP40) MEMBER B9 **(DNAJB9) IS NEGATIVE.**


Thank You
For Your
Attention